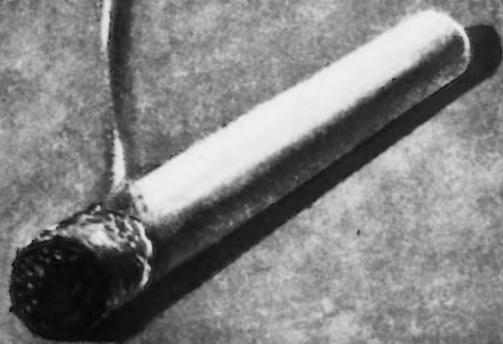
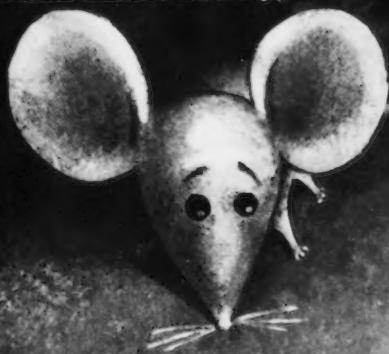


May 1955 Vol. 5 No. 3

# Ca

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*check  
mitigate  
or prevent*

The stated objective of the epidemiologist is to "check, mitigate or prevent epidemic and endemic diseases." Pandemic lung cancer, with the most rapid increase ever ascribed to a noninfectious disease, might—some would say *WILL*—yield to established epidemiological methods.

In the systematic search for environmental etiological factors, tobacco smoke is now widely accepted as associated with the increasing incidence of lung cancer. Other factors of modern civilization that have been incriminated are coal and oil smoke; automobile exhausts; and arsenic, chromate-, nickel carbonyl-, and radiation-bearing dusts. Possibly two or more of these or other unknown factors operate as cocarcinogens.

The evidence incriminating cigarette smoke has been aspersed by some as "only statistical." They demand "scientific experimental proof"—isolation of a smoke constituent demonstrated to be carcinogenic to the human lung.

Many endemic and epidemic diseases in the past were at least partially controlled without such complete and final etiological knowledge—scurvy, smallpox, cholera, and "black death." Similarly lung cancer can now be at least partially controlled by application of existing etiological knowledge.

Of the factors under etiological suspicion, cigarette smoke appears to be associated with the greatest number of cases of lung cancer and, fortunately, is the only one over which the individual can exercise his nature-endowed free will.

The prudent course for the doctor when asked about smoking is, therefore, to acquaint his patients with the known statistical and other facts; to urge men more than 40 years of age, and especially the heavy smokers, to have frequent physical examinations, including semiannual chest roentgenograms; and to impress upon his younger patients the advantages the nonsmoker has not only concerning lung cancer and chronic bronchitis but also concerning vascular diseases, particularly coronary-artery disease and peptic ulcer, and, above all, concerning longevity.

What youth will fail to be impressed by the fact that his chance of having lung cancer after age 45 is increased fiftyfold by smoking twenty-five or more cigarettes a day?

With active propaganda for early diagnosis and against the suspected etiological agents, the family doctor can do most to "check, mitigate or prevent" lung cancer.

*Cover—*

Nothing is more gentle than smoke,  
nothing more frightful.

Victor Hugo, *Les Misérables*.



# NEWSLETTER

MAY, 1955

## AMERICAN CANCER SOCIETY ANNUAL MEETING

Lung Cancer: "Lung Cancer -- The Problem of Early Diagnosis," a color teaching film financed by N.C.I. and A.C.S., was premiered at the meeting. Prints are available to medical groups throughout the country. In it, Herbut (Jefferson Med. College) demonstrates cytology, which in his experience has proved 85.6 per cent accurate in finding 603 cancers in a series of 706 patients.

Bronchoscopic biopsy was 30.6 per cent accurate in the same series. Ochsner (Tulane U.) complained that too often lung-cancer patients with pneumonitis are diagnosed as having viral pneumonia and treated for weeks and months before the true diagnosis is established. Graham (St. Louis) urged surgeons to be more alert in diagnosing lung cancers; and Overholt (Boston) said that 75 per cent of lung cancers are confined to their site of origin while they are symptomless and unsuspected and that less than 20 per cent are localized when symptoms have appeared.

Cameron (A.C.S.) cited these probabilities of young American males developing lung cancer; generally -- 1 in 50; never smoked -- 1 in 170 to 190; light to moderate cigarette smoker, 1 in 40 to 45; pipe or cigar (but no cigarette) smoker, 1 in 150 to 190; heavy (pack or more a day) cigarette smoker, 1 in 15 to 20. He said the Cancer Society has earmarked \$500,000 as a special fund for the support of investigation into the causes of lung cancer. He suggested that if carcinogens are found in cigarette-smoke condensate, the search for their origin will include the cigarette wrapper, crude leaf, insecticides, and additives.

Horn (A.C.S.) raised these considerations in connection with the rocketing lung-cancer rate among men and more static situation among women: twenty years ago a city survey showed 61 per cent of men smoked cigarettes as against 17 per cent of the women; last year the figures were 68 per cent for men and 43 per cent for women; the increase in smok-

ing was most prominent among women of low incomes and less than 35; only one in five women older than 45 smokes at all; a women smoker consumes only two thirds what the male does. In other words, women start smoking later in life, fewer smoke, they smoke less, they haven't been smoking very long -- and these differences are more marked among older folk who've reached the lung-cancer age.

Hammond (A.C.S.) said he had found no evidence to change his opinion that cigarette smoking has been shown "beyond a reasonable doubt" to be a major cause of lung cancer. He said there are no "safe" limits to smoking short of stopping completely.

[Meanwhile, at a concurrent meeting of the American Chemical Society in Birmingham, Lefemine and others (Cancer Institute at Miami) reported isolating 3,4-benzpyrene, carcinogenic to mice, from burned cigarette papers.]

Runyon (A.C.S.) said that if present cancer rates continue: Cancer will strike one in four Americans; 40 million now alive will have the disease; 24 million will die of it.

Popma (Boise, Idaho) called for a long-range program against cancer quackery -- "an unceasing battle against such men or groups of men who are exploiting the cancer patient and who are filling our cemeteries with tombstones as monuments to inefficacy of their treatment." He was appointed to head a committee to help foreign countries develop organizations similar to the American Cancer Society.

The Board of Directors, on motion of Adams (Research Committee Chairman), voted to invite the National Cancer Institute, National Heart Institute, and American Heart Association to join the Society in publicizing the possible harmful effects of cigarette smoking.

Ledermann (French National Institute of Demographic Study, Paris) told the United Nations Conference on Population in Rome that alcohol appears to act as a "multiplying factor" in potentiating carcinogens, including any that may reside in cigarette tobacco. Basing his observation on 3500 cancer cases, he said excessive use of alcohol and tobacco appear to multiply each other's carcinogenic powers. He expressed the opinion that tobacco was an etiological factor in cancers of the oral cavity, lung, and face skin. He found that if nondrinking smokers run five times the nor-

(Continued after page 108)

# *a Bulletin* **Ca** *of* *Cancer* *Progress*

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# Keeping up a

## Primary Breast Cancer

Carcinoma of the breast is fundamentally a problem of cancer outside the breast. When the disease is confined to the breast, simple mastectomy is often sufficient. When the disease has spread beyond the breast, radical mastectomy cures only those patients with disease confined to the chest wall or axilla. The Halsted radical mastectomy is of greatest value when the tumor has spread by lymphatic routes only. However, it is now apparent that blood-borne metastases are all too common, even at the earliest stages. Breast lesions are not considered operable when: (1) more than one third of the skin of the breast is involved by edema, (2) satellite nodules are present in the breast skin, (3) the carcinoma is inflammatory, or (4) the cancer is locally far advanced. Because a large number of breast cancers are already beyond the scope of surgical removal when first seen and because radical operation may actually shorten the survival time of some patients, simple mastectomy and radiotherapy are recommended for these reasons: Simple mastectomy is adequate for most lymph-node-free cases of breast cancer. The procedure is safer and has a lower morbidity rate than radical surgery. Complications such as postoperative arm edema are fewer. Prolonged handling of tissues is avoided, reducing the chance of cancer dissemination. The patient may resume useful work earlier than after the radical procedure. Postoperative radiation therapy does not delay removal of a potential solitary focus in the breast. The five-year absolute-survival rate is as good

as that generally reported with radical surgery. Disadvantages include (1) failure to control radioresistant but locally removable extramammary cancer, (2) hazards to the lung apex in patients with active upper-lobe tuberculosis, (3) probable failure to secure adequate radiation dosage in obese patients, (4) possible tissue injury if the procedure is not done meticulously, and (5) prolongation of therapy two to three weeks after surgery.

*Garland, L. H.: The rationale and results of simple mastectomy plus radiotherapy in primary cancer of the breast. Am. J. Roentgenol. 72: 923-941, Dec., 1954.*

## Environmental Carcinogens

The number of industries utilizing substances from which it is known or suspected that carcinogens may be derived is increasing, and the occupationally and environmentally exposed members of the population are, as a corollary, increasing. Carcinogenic substances incidental to industrial procedures represent a hazard both to those occupationally exposed and to the population in general. The potential carcinogenic materials may be classified on the basis of their nature, their environmental site, and the target tissues responding to them.

Their natural state may be chemical, physical, or biological. (The chemical agents fall into organic and inorganic groups; representative of the former are the aromatic amino and azo compounds, coal tar and its derivatives, and petroleum and its by-products. The inorganic chemical agents are exemplified by arsenic, chromium, and nickel. The physical group includes various sorts of ionizing radia-

# with Cancer



tion, even including the ubiquitous effect of ultraviolet irradiation from exposure to sunshine. There are also a few cancers of parasitic origin with occupational implications, particularly the cancer of the urinary bladder secondary to schistosomiasis seen in the farmers of lower Egypt.)

Their environmental site may be in the atmosphere, in the soil, or in the water. The tissues responding to them may be at the site of initial contact or in organs or organ systems concerned with their metabolic and eliminative processes. The capacity of neoplastic response is something more complex than the sequence of simple exposure of the tissue or organ that may so respond to the environmental agent capable of evoking such a response. Assuming that a certain substance has carcinogenic properties, the development of a neoplasm, as well as the duration of the latent period, will be determined by the product of the several factors of potency, time and intensity of exposure, and individual responsiveness. Of these the last is by far the most important, with the potency of the agent being next in significance. In some industries individual susceptibility as shown by the development of premalignant lesions provides a method for mass screening that filters out the employees to whom the occupation is a hazard. An outstanding example is the development of papillomas of the urinary bladder in aniline-dye workers, 30 to 40 per cent of whom will have this precancerous process. Detection and eradication of the papillomas by cystoscopic technique and removal of the employees so affected from contact with the carcinogens can re-

duce the incidence of cancer of the bladder from this cause to nearly zero. It is, therefore, concluded that the control of these environmental factors seems entirely practical on the basis of current industrial hygiene and toxicological practices. An awareness on the part of industrial physicians is the necessary starting point for the protection of those environmentally exposed.

*Macdonald, I.: Environmental factors of occupational origin related to carcinogenesis. J.A.M.A. 157: 5-7, Jan. 1, 1955.*

## Cancer Control

The expenses of cancer research must be met by public funds obtained by taxation or solicitation. A mistake in the early days of modern cancer research was spreading the available funds too thinly and too widely in the hope of statistically increasing the chance of discovery of the fundamental nature of the disease. These multiple, small grants are now being replaced by institutional grants under which experts in the several related fields work in unison in well-equipped laboratories and hospitals. The cancer cell can be attacked just as another invading microorganism, like the pneumococcus and the tubercle bacillus, and is, like them, potentially susceptible to selective chemical destruction. The cancer cell has now been shown experimentally to fulfill Koch's postulates, thus justifying the chemotherapeutic approach to the control of cancer. Chemotherapeutic modalities successfully used to date include estrogens, androgens, ovarian and testicular ablation, adrenalectomy, hypophysectomy, antimetabolites, adrenocortical hormones, adrenocortico-

tropic hormone, and 6-mercaptopurine. These successes justify the hope of controlling cancer through chemotherapy.

*Rhoads, C. P.: Pitfalls and progress in cancer control. Ann. Int. Med. 41: 1115-1123, Dec., 1954.*

### Ovarian Neoplasms

The ovarian dermoid cyst, or cystic teratoma, constitutes approximately 15 to 20 per cent of all ovarian neoplasms. This cystic neoplasm is ordinarily benign and composed primarily of well-differentiated ectodermal elements as compared to the malignant, solid teratoma containing a conglomeration of all three germinal layers. It is bilateral in about 20 per cent of the reported cases. Three cases are reviewed in which malignant disease developed in the epithelial elements of ovarian dermoid cysts. When a dermoid undergoes malignant transformation, it is usually a squamous-cell epithelioma, except in very rare instances, as in one of the three cases presented that showed osteogenic sarcoma and leiomyosarcoma. The prognosis is extremely poor in these malignant transformations, particularly if capsule perforation has occurred. The frequency of ovarian dermoids, their bilateral proclivity, and the extremely poor prognosis when malignant change occurs despite its low incidence emphasizes the necessity of careful examination of both ovaries whenever surgery on cystic teratomas is undertaken.

*Burgess, G. F., and Shutter, H. W.: Malignancy originating in ovarian dermoids; report of three cases. Obst. & Gynec. 4: 567-571, Nov., 1954.*

### Total Gastrectomy for Gastric Cancer

From data reported, it can be concluded that total gastrectomy for cancer of the stomach does not increase the five-year-survival rate and is not always justified. A high incidence of cures results only when surgery is performed early for malignant tumor that is limited to the stomach. Initial symptoms include epigastric pain and discomfort, anorexia, and nausea. Vomiting, weight loss, hematemesis or melena, and anemia are often late manifestations. Achlorhydria is noted in

about one third of patients. Roentgen-ray diagnosis is accurate in more than 90 per cent of instances. Cytological and peritoneoscopic studies are valuable when the radiological procedure fails. Gastroscoptic examination is employed to differentiate gastric ulcers, gastric polyps, and chronic gastritis. Malignant tumors of the stomach may metastasize to regional lymph nodes, blood vessels, and adjacent organs. Cancer always extends beyond the visible and palpable limits of the lesion. To extirpate cancer complete excision of regional vascular- and lymphatic-drainage areas is necessary but is practically impossible. Total gastrectomy should be employed only when the radical procedure is necessary to resect all diseased tissue and complete removal seems possible. A series of 202 cases of total gastrectomy is reported, of which 184 were for malignant tumors. As would be expected, the mortality rate in the earlier group of cases from 1927 to 1943 was high (34.6 per cent). With experience in operative technique and improvements in preoperative preparation and postoperative care, the mortality rate in the later group of 127 cases was decreased to 8.7 per cent.

*Marshall, S. F., and Uram, H.: Total gastrectomy for gastric cancer: effect upon mortality, morbidity, and curability. Surg., Gynec. & Obst. 99: 657-675, Dec., 1954.*

### Radical Retropubic Prostatectomy for Cancer

It is estimated that in the United States there are from 195,000 to 1,500,000 men who have cancers of the prostate in a stage early enough to warrant attempt at cure by surgery. The cure rate of cancer of the prostate throughout the country is low for two reasons. 1. In the majority of cases the disease progresses so silently that by the time it causes symptoms it has already spread and become locally inoperable. The only defense against this factor is an educational program for an annual physical check-up with a rectal examination of all men more than 50. 2. Although radical perineal prostatectomy in early cases has produced results superior to those of other methods, the operation has never been

popular owing to the major complications that sometimes accompany its use. To mitigate this situation the author recommends radical retropubic prostatectomy for total extirpation of the cancerous prostate for the following reasons, based on the results of a series representing more than two hundred cases: The retropubic operation gives results that are just as good as the radical perineal procedure. There is no greater mortality, the operation is easier to perform, and there is less danger of rectal fistulas. Postoperative incontinence is about the same as that following the perineal operation; in addition, abdominal exploration or dissection of the pelvic nodes can be carried out. The injection of radioactive gold, if extraprostatic spread is found, can be done in conjunction with it. The author's technique of radical retropubic prostatectomy is described in detail with excellent drawings.

Chute, R.: *Radical retropubic prostatectomy for cancer. J. Urol.* 71: 347-372, March, 1954.

### Prevalence of Prostatic Cancer

Microscopic evidence of carcinoma has been found in 75 per cent of the prostates of men who died in the ninth decade and in all of a small group in the tenth. Apparently, if life is long enough, every prostate will show some degree of malignant development, but the disease remains localized and symptomless in a large proportion of men. Franks and others refer to such localized tumors as "latent" cancer, implying that they have the capacity for more vigorous and aggressive growth. The old term "locally malignant," which implies no more than it says, seems preferable.

Anonymous: *Local malignancy in prostatic cancer. Lancet* 2: 1064, Nov. 20, 1954.

### Bilateral Independent Mammary Carcinoma

Careful criteria for definition of bilateral independent mammary cancers must be observed. The true incidence of bilateral independent mammary carcinoma

appears to be less than 5 per cent. The survival rates for patients treated for bilateral independent mammary carcinoma are much better than for those with unilateral lesions. If routine simple mastectomy of the uninvolved breast were added to the procedure of radical mastectomy for unilateral cancer, the clinical course of the patients would be favorably affected in less than 1 per cent of cases so treated. At the present time there appears to be no valid indication for "prophylactic" simple mastectomy of the uninvolved breast.

Guiss, L. W.: *The problem of bilateral independent mammary carcinoma. Am. J. Surg.* 88: 171-175; disc. 175-177, July, 1954.

### Malignant Melanoma

Failure to seek prompt medical advice and improper initial treatment are principally responsible for the low five-year-survival rate in persons with malignant melanoma. Recurrence after removal of the primary tumor at some other institution has been reported in 80.5 per cent of the patients with this condition seen at one hospital and in 64 per cent of the patients in another series. Records of Vanderbilt University Hospital for the last twenty-five years show that 66 per cent of sixty-three patients treated for malignant melanoma had previously received treatment elsewhere. Cauterization or desiccation had been used in 24 per cent of these patients, and this fact indicates that no benign pigmented mole should ever be treated in this manner. The nature of the lesion, whether an infectious or squamous-cell wart, a benign pigmented mole, or a malignant melanoma, should be established by microscopic section before any treatment is given, because the proper treatment for a malignant lesion cannot be instituted if the tissue has been destroyed by cautery. The fact that the number of patients seeking treatment for moles is increasing makes it more important than ever that the initial treatment should be adequate. Both benign and malignant melanin-bearing lesions may appear clinically nonpigmented; thus, in 20

per cent of the malignant melanomas in this series no pigment could be detected on physical examination. Ulceration, found in 44 per cent of the skin lesions, is strongly indicative of malignant disease. Only 25 per cent of the tumors were primary, metastasis having already occurred in the other 75 per cent when the patients were first seen at the Vanderbilt University Hospital. The lesions were so far advanced in twenty-three patients that no operative treatment, apart from a simple biopsy, could be given. The other forty patients were treated by excision of the lesions, with or without skin grafting and with or without regional node dissection. The radical excision, in-continuity procedure was not used in any of the cases. Cures have apparently been obtained in twelve of these patients, with survival times ranging from five to twenty-one years. Although the chances of obtaining a five-year survival with adequate treatment can be considered good, a five-year-survival period is not long enough for accurate evaluation of the results in malignant melanoma, since two patients who had survived for five years later succumbed to recurrences six and one-half and eight years respectively after operation.

Riddell, D. H., and McSwain, B.: Malignant melanoma: review of sixty-three patients. *Am. Surgeon* 20: 827-833, Aug., 1954.

### **Carcinoma of the Rectum at Advanced Age**

A steadily increasing number of patients of advanced age with carcinoma of the rectum is being encountered. Abdominoperineal resection may be warranted even in the ninth decade, if lesions are not too far advanced. The main object is to provide the greatest possible comfort for remaining life. The patient should be fairly active and alert, able to care for himself, and willing to have a permanent colostomy. The family must be made aware that operative mortality is 25 to 35 per cent. With fair exercise tolerance, heart disease need not be a contraindication, but if the lesion is extensive, with

local infiltration into the pelvis or with demonstrable metastases, there is nothing to be accomplished by palliative resection. Preparation of the bowel includes a cathartic and two days of colonic irrigations, with an antibiotic drug over the same period. Activity is continued. Spinal anesthesia may be employed, or nitrous oxide and oxygen, with succinylcholine hydrochloride for relaxation. Abdominoperineal resection is done in one stage, closing the wound with nonabsorbable sutures. The legs are bandaged immediately. An indwelling catheter is utilized for a week after operation but ambulation is usually begun within two days.

Cattell, R. B.: Carcinoma of the rectum at advanced age. *S. Clin. North America* 34: 721-727, June, 1954.

### **Relationship Between Fibrocystic Disease and Carcinoma of the Breast**

A follow-up of fibrocystic disease of the breast has been under way for some years at the tumor clinic of the Montreal General Hospital as part of a general follow-up of all patients treated at the Hospital for malignant disease, as well as of those with benign conditions suspected of being precancerous. Fibrocystic disease of the breast is generally regarded as precancerous by investigators who use histological methods of investigation; those who rely on clinical findings and prolonged follow-up of individual patients, however, find that it is not precancerous. The clinical approach was used in this study, designed as an interim report on the information already obtained in the Montreal program. The records of the tumor clinic and the pathological department showed (1) that the incidence of previous operations for fibrocystic disease in 313 patients with proved carcinoma of the breast was 2.23 per cent, (2) that the incidence of previous operations for fibrocystic disease in a control series of 300 women of about the same age distribution was 3 per cent, and (3) that carcinoma of the breast has not developed in any of sixty-four patients operated on for known fibrocystic disease with a follow-up of from eight to twenty-

three years. The pathological findings in these sixty-four patients were: cystic disease alone, forty-one; cystic disease with intraductal papilloma, six; cystic disease with benign neoplasia, eight; cystic disease with fibroadenoma, eight; and cystic disease with cystadenoma, one. Biopsy, simple removal of the tumor mass, or segmental resection was performed in thirty-three; the other thirty-one were subjected to simple mastectomy (bilateral in five). The results in each of the three groups agree closely with those given in published reports of larger series of patients with fibrocystic disease followed over a period of years.

Palmer, J. D., and Martin, S. J.: *The relationship between fibrocystic disease and carcinoma of the breast.* *Canad. M. A. J.* 71: 259-261, Sept., 1954.

### Concentration of Cells from Body Fluids for Cytological Study

A method of concentrating malignant-tumor cells and of separating them from blood was reported by Fawcett, Vallee, and Soule in 1950. This method is based on differences in the specific densities of various cell types. It involves centrifugation of the cell suspension in a concentrated solution of albumin, on which the malignant cells float and through which the erythrocytes are forced down. The procedure as originally described by Fawcett and co-workers has been slightly modified in this study for routine use. Thirty specimens of pleural, peritoneal, and pericardial fluid, with or without gross blood, were studied. Sixteen of these were interpreted as negative; two, as suspicious; and ten, as positive for malignant-tumor cells. The direct smears of all specimens were reviewed, comparing the original sediment with the flotation specimen. In ten of the thirty specimens sufficient blood was present in the original sediment to interfere with interpretation. In all of these, flotation succeeded in eliminating the blood as a confusing element, although a few red blood cells remained. The ease with which interpretation could be made was greatly enhanced in all the flotation specimens. In one specimen there

was a clearly positive flotation smear, but it was impossible to detect malignant cells in direct smears or in sections prepared from paraffin blocks of the original sediment. In eleven of the specimens, nine of which were positive, the concentration of nucleated cells was strikingly increased in the flotation layer. In some there were ten to fifteen times as many malignant cells per field as in the direct smears of the original sediment. In twenty-eight out of thirty flotation specimens, the additional time of forty-five to sixty minutes before fixation, the exposure to the albumin, and the two saline washes resulted in no detectable morphological degenerative changes in the cytoplasm or nuclei of the cells. The author concludes that the method is practical as a routine laboratory procedure for cytological examination of bloody, purulent, or turbid fluids.

McGrew, E. A.: *Concentration of cells from body fluids for cytological study.* *Am. J. Clin. Path.* 24: 1025-1029, Sept., 1954.

### Second-Look Procedures for Cancer

The second look in cancer surgery is a new concept employing systematic re-operations to remove asymptomatic, residual cancer of the stomach, rectum, or colon with lymph-node metastases. Six to eight months after the original excision, while the patients still show no clinical evidence of residual cancer, a second operation is performed and any residual cancer found is removed, if possible. If cancer is found at this second-look operation, third and fourth operations are carried out subsequently at similar intervals of time until no more cancer is found. In some of the 103 patients who had gastric, colic, or rectal cancers with lymph-node involvement, further exploratory operations were performed after the second-look operation, so that, in all, 141 operations were done after the original excision. Six patients with residual cancer at the second operation were finally found to be free from cancer at some subsequent operation. They are still alive and have no evidence of residual cancer. One of the six patients had cancer of the stomach;

one, cancer of the rectum; and four, cancer of the colon. The second-look procedure would appear to exhibit greatest promise in patients with colic cancer. The authors feel that sufficient time has not elapsed to establish or disprove their assumption that residual abdominal cancers may often be completely resected. Their early experience suggests that this may be possible in at least some types of residual cancers. In all the patients in whom the second-look operation proved effective, residual cancer was limited to one or a few lymph nodes and to one area of the abdomen. For patients with this type of residual cancer, the second-look procedure may prove to be a crucial addition to therapy.

Wangensteen, O. H.; Lewis, F. J.; Arhelger, S. W.; Muller, J. J., and MacLean, L. D.: An interim report upon the "second look" procedure for cancer of the stomach, colon, and rectum and for "limited intraperitoneal carcinosis". *Surg., Gynec. & Obst.* 99: 257-267, Sept., 1954.

### Total-Body Irradiation

Nitrogen mustard (HN2) and tri-

ethylenemelamine (TEM) are spoken of as "radiomimetic" agents because their effect is similar to radiotherapy in the treatment of several forms of cancer. Where both agents are of known effectiveness, nitrogen mustard is usually preferred for generalized cancer because the dose of total-body irradiation is believed to be limited to an ineffective level by radiation sickness and bone-marrow depletion. The validity of this preference was tested in ten patients having advanced cancer. It was found that large doses of total-body radiation (up to 150 r in one case) were no more dangerous than HN2 or TEM, which produced malaise of varying severity, whereas none of the patients receiving radiation mentioned any changes in symptoms. It would appear that total-body radiation may be preferable for treatment of some malignant neoplasms currently being treated routinely with radiomimetic agents.

Loeffler, R. K.; Collins, V. P., and Hyman, G. A.: Comparative effects of total body radiation, nitrogen mustard, and triethylene melamine on the hematopoietic system of terminal cancer patients. *Science* 118: 161-163, Aug. 7, 1953.

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### Occam's Razor

It is theoretically possible for both smoking and the development of bronchial carcinoma to be themselves related to some third common factor. In view of the apparently linear increase in the mortality from lung cancer with increasing tobacco consumption, we should need to postulate that this third factor was also linearly related both to smoking and to the risk of developing the disease. In the absence of positive evidence that such a factor exists it is more reasonable to adopt the philosophical principle of Occam's razor, which has served science so well in the past, and to proceed on the basis of the simplest explanation; that is, that the more people smoke the more likely they are to develop carcinoma of the lung.

Doll, R.: In *Milroy Lectures*, Royal College of Physicians, London, Feb. 10, 12, 1953.



## a glance . . .

one-minute abstracts  
of the current literature  
on cancer . . .

### **Tobacco as Cause of Lung Cancer**

Nonsmokers constituted only 1.4 per cent of 979 men with squamous-cell cancer in a review of 1104 proved cases of lung cancer. Among sixty men with adenocarcinoma 10 per cent were nonsmokers. Interviews with 6307 patients with lung cancer revealed that 1.5 per cent were nonsmokers as compared with 16.3 per cent nonsmokers found among 6616 "control patients" who were interviewed by the same investigators. Among the different factors pointing to an association between smoking and lung cancer, the most impressive are that the data conform to clinical experience and that lung cancer so rarely occurs in a nonsmoker. This study is in agreement with Doll's findings, in that the tobacco data are compatible with the hypothesis that, in the absence of smoking, there is no appreciable difference in sex incidence or in urban-rural distribution of lung cancer. Establishing tobacco smoking as a cause of lung cancer does not deny the etiological significance of other factors, such as predisposition, occupational exposures, and air pollution. However, the author believes that specific carcinogens are present in tobacco smoke, as evidenced by

condensed cigarette smoke inducing epidermoid cancer of the skin in nearly one half of the animals to which the tar was applied. Once a specific carcinogen or carcinogens have been identified, steps should be taken to remove these either by changing the manufacturing process of tobacco or by employing a specific means of filtering the smoke. In the attainment of this goal, together with a moderation of general smoking habits, lies the most practical measure leading to the reduction of primary lung cancer.

*Wynder, E. L.: Tobacco as a cause of lung cancer, with special reference to the infrequency of lung cancer among non-smokers. Pennsylvania M. J. 57: 1073-1083, Nov., 1954.*

### **Preclinical Bronchogenic Carcinoma**

Of a total of seventy-seven proved cases of bronchogenic carcinoma discovered in photofluorographic surveys, fifty were considered preclinical, since the patients had not sought medical attention and the survey was the only means for detection of the tumor. The rate of occurrence of bronchogenic carcinoma was 30 per 100,000 persons examined, with the incidence in males more than ten times that in females. Prevalence in persons more than 45 years of age was more than fifty times

that in persons less than 45. Only 18 per cent of the seventy-seven patients survived the follow-up period of three months to six years. Previous films were available in twenty-two cases and had been reported as normal. On review, eleven of these were found to have some indication of the disease, while the other eleven showed no abnormality. All of the patients in the latter group have died. Of the eleven patients whose films were at first erroneously interpreted as normal, four had resections and are alive eight to fifty-two months following surgery, while a fifth survives without surgery. Although the lesions were discovered in surveys of the general population, only 10 per cent of the patients were found to be completely asymptomatic on close questioning. The findings suggest the need for more frequent chest films in males more than 45, with comparison of previous films at each reading and a high index of suspicion when any abnormality appears. In patients with symptoms but with normal roentgenograms, careful clinical study is indicated.

*Boucot, K. R., and Sokoloff, M. J.: Preclinical bronchogenic carcinoma. Am. Rev. Tuberc. 69: 164-172, Feb., 1954.*

### **Surgery for Solitary Lung Lesions**

On the basis of the authors' experience, it is believed that thoracotomy and thorough exploration of the hemithorax should be done for a patient with a solitary pulmonary lesion. A complete cardiopulmonary evaluation is also warranted. Lateral and oblique roentgenograms should be made, since the existence of a solitary lesion does not eliminate the possibility of multiple lesions, especially with metastatic carcinoma. Calcification does not always indicate tuberculoma or granuloma, since the process occurs also with sarcomas and hamartomas. At operation, frozen sections are made and benign lesions are excised locally. With malignant growth, lobectomy is performed if regional lymph nodes do not reveal metastasis; pneumonectomy is performed if the nodes are involved.

*Meckstroth, C. V.; Andrews, N. C., and Klassen, K. P.: Surgery for solitary lesions of the lung. A. M. A. Arch. Surg. 69: 220-232, Aug., 1954.*

### **Pulmonary Neoplasm Research Project**

Since, at present, surgery offers the only hope of survival to the patient with lung cancer, curability depends on resectability. Among the factors involved in resectability are the presence or absence of symptoms, the promptness with which persons seek medical advice in the presence of symptoms, the alertness of physicians in advising adequate studies, the frequency with which persons report for photofluorograms, their co-operation in obtaining study when there is evidence of roentgenographic abnormality, and those factors that involve prompt and adequate treatment. In an effort to delineate the characteristics of "curable" cancer of the lung, the Philadelphia Pulmonary Neoplasm Research Project was set up on December 4, 1951. The plan of study calls for following 6000 men 45 years of age and older by 70-mm. photofluorograms, both inspiratory and expiratory, every six months for a period of ten years. A questionnaire covering symptoms and smoking habits is completed at each visit. After a follow-up period of four to thirty-four months, thirty-seven proved lung cancers have been detected among the 3945 men who entered the study during the first two and one-half year period. Not one of these occurred among the 559 nonsmokers. Worsening cough and hemoptysis were the most significant symptoms.

*Boucot, K. R.; Carnahan, W.; Cooper, D. A.; Neilson, T., Jr.; Ottenberg, D. J., and Theodos, P. A.: Philadelphia Pulmonary Neoplasm Research Project; preliminary report. J.A.M.A. 157: 440-444, Jan. 29, 1955.*

### **Smoking and Pulmonary Carcinoma**

An investigation comprising 351 patients with pulmonary carcinoma in whom the diagnosis was confirmed histologically and 494 patients with pulmonary cancer not verified by biopsy is reported. The control material consisted of 315 patients. Both groups consisted predominantly of men. It was found that the patients with pulmonary carcinoma were almost all smokers who had smoked heavily for

decades. In comparison with the control material, they started smoking earlier, often in childhood, and smoked continuously for about forty years, an average of eight to ten years longer than patients free from pulmonary carcinoma. The conclusions refer principally to men and the significance of these circumstances in the genesis of pulmonary carcinoma.

Koulumies, M.: *Smoking and pulmonary carcinoma. Acta radiol.* 39: 255-260, March, 1953.

### Etiology of Lung Cancer

From statistical evidence that cancer of the larynx has not increased in frequency during the period in which cancer of the bronchi and lungs has increased so enormously it is deduced that no inhaled carcinogenic substance, including cigarette smoke, can be a vital factor in the etiology of cancer of the respiratory tract. Otherwise it would be necessary to make the improbable assumption of a difference in sensitivity of the mucous membranes of the larynx and of the bronchi to an inhaled carcinogen. It is concluded that some hidden and hitherto unsuspected factor is largely responsible for the increase in cancer of the lung.

Maxwell, J.: *The incidence of cancer of the larynx in relation to the incidence of cancer of the bronchi. Lancet* 1: 193, Jan. 22, 1955.

### Mortality from Cancer of the Lung in Canada

The statistics on deaths from lung cancer in Canada for the years 1931 to 1952 were analyzed to assess any changes that might have occurred in the mortality rates and to compare them with those reported in other countries. The deaths given in the annual vital statistics reports for Canada are coded according to the International List of Causes of Death, but, since various revisions (the fourth, fifth, and sixth) of this list were made during the period under review, the figures for the years 1931 to 1940 cannot be combined with those for later years without qualification. Conversion factors, however, were provided by which the data collected for the years

1941 to 1949 could be made comparable to those for 1950 to 1952. The adjusted figures show that deaths from lung cancer have increased for both sexes from 2.2 per cent of all cancer deaths in 1931 to 8.7 per cent in 1952. The 1952 figure agrees closely with the value of 8.1 per cent given by Dorn for the United States. Correction of the figures to allow for changes in the age structure of the population showed that deaths from lung cancer increased from 2.4 per 100,000 population in 1931 to 10.7 in 1952. The standardized lung-cancer-death rate for men during the same period rose from 3 to 17; for women, it rose from 1.6 to 3.7. The ratio of men to women dying of cancer of the lung has increased from 1.9 to 1 in 1931 to 4.9 to 1 in 1952.

Phillips, A. J.: *Mortality from cancer of the lung in Canada; 1931-1952. Canad. M. A. J.* 71: 242-244, Sept., 1954.

### Bronchogenic Carcinoma

A series of 181 patients with histologically proved bronchogenic carcinoma observed at the Richmond, Virginia, Veterans Administration Hospital from 1946 to 1953 is reported. In ninety-five (52.5 per cent) the lesions were inoperable at the time of diagnosis. The remaining eighty-six were subjected to thoracotomy, but in thirty-two (17.7 per cent) the tumors were found to be nonresectable. Thus 127 (70.2 per cent) of the growths were inoperable and fifty-four (29.8 per cent) were resectable. This resectability rate is about the same as that reported in the literature. Of twenty lesions that were discovered during the silent phase, fifteen were malignant. Eleven of the fifteen patients who had silent discrete peripheral malignant lesions were followed for an average of sixteen months from the time of discovery of the lesions by roentgen-ray examination until the time of surgery. By the time of surgery, one of these lesions was inoperable and six were clinically symptomatic or showed definite enlargement of the mass. Only four were explored in the absolutely silent phase. These eleven tumors represent the important

group, of which Overholt said that they are always resectable and that 75 per cent are resected with a chance of a cure. They also tend to demonstrate how long the silent phase is in some of these tumors. Survey films are the most useful method for detecting these lesions while silent. Men more than 40 years of age should have a roentgenogram of the chest every six months if improvement in resectability rate is to be attained. Once a lesion is detected its true nature should be determined without delay. An aggressive approach to carcinoma of the lung is justified by results of surgical treatment.

Brown, J. B.; Wilson, J., and Coleman, F. P.: A statistical analysis of one hundred eighty-one consecutive cases of bronchogenic carcinoma. *J. Florida M. A.* 41: 270-275; disc. 275-276, Oct., 1954.

#### **Management of Lung Tumors Found in Roentgenological Surveys**

A coin shadow in the lungs usually represents either a tuberculoma or a neoplasm but attempts to categorize the type of tumor on roentgen-ray examination are neither reasonable nor desirable. Any persistent, unexplained lesion, whether large or small, deserves immediate and aggressive investigation. A wedge resection is used for biopsy. If the lesion proves to be carcinoma, total pneumonectomy is indicated. With bronchial adenoma, the choice between lobectomy and pneumonectomy is controversial. Some bronchogenic carcinomas are indolent for years, so that the establishment of the presence of a lung lesion for an extended period of time does not necessarily rule out lung cancer. An enlarged hilar shadow should be investigated bronchoscopically. Biopsy of the fat pad over the anterior scalenus muscle will sometimes reveal lymph nodes containing metastatic tissue establishing the true nature of the lesion. Exploratory thoracotomy is recommended without hesitation if these methods do not establish a satisfactory diagnosis. The atelectasis that occurs with tuberculosis may mask the development of a concomitant carcinoma. The tendency of lung cancer to mimic viral pneumonia is mentioned as one of the most important single factors in the delay

of proper treatment. Patients with such a condition are usually symptomatic, however. For asymptomatic individuals the author recommends biannual full-sized roentgenograms of the chest as the best method of early detection.

Blades, B. B.: Surgical management of tumors of the lung discovered in x-ray surveys. *J.A.M.A.* 154: 196-198, Jan. 16, 1954.

#### **Bronchogenic Carcinoma**

In a review of 517 cases of bronchogenic carcinoma, only 30 per cent of patients were considered "operable" at the time they were diagnosed at the Albany Hospital. The remaining 70 per cent of patients had metastases or were in poor general condition and therefore unsuitable for operation. About 40 per cent of patients who underwent operation were discovered to be suitable for surgical resection, so that, when a diagnosis of bronchogenic carcinoma was made, there was about one chance in ten that an attempt could be made to obtain a surgical cure. In the authors' series, 90 per cent of the cancers that were identified histologically were either squamous-cell or anaplastic types. There was the expected predominance of male patients. The commonest time of onset of symptoms was in the fifth and sixth decade. The commonest single location of all tumors was in the right upper lobe. In 220 cases in which diagnosis was made more than five years before the termination of the study, five patients (2.3 per cent) survived for five years or more. There were no five-year survivors among those patients who were found to have lymph-node metastasis at the time of operation.

Ehler, A.; Stranahan, A., and Olson, K. B.: Bronchogenic carcinoma; a study of 517 cases. *New England J. Med.* 251: 207-213, Aug. 5, 1954.

#### **The Serious Problem of Bronchial Cancer**

Numerous experiments by different investigators have conclusively established the fact that tobacco tar is capable of producing cancer, though its carcinogenic properties are less than those of coal tar.

Efforts have been made to identify the carcinogenic substance or substances in tobacco smoke, but they are still unknown; nicotine, however, can be definitely eliminated as a causative agent. Physicians should recognize the gravity of the problem and, even if not willing to set an example by abstaining from cigarette smoking, should refrain from adversely influencing persons about to give up the habit by expressing skepticism in regard to the connection between cigarette smoking and pulmonary cancer. A fatalistic attitude leading to the conclusion that persons who have been confirmed cigarette smokers for years will not be saved from cancer by giving up the habit is equally unjustified, because experiments have shown that, in cases in which as many as thirty applications of cigarette tar have been given to mice without harmful effect, a thirty-first application has resulted in the development of cancer. The cause of cancer is always complex, and many factors may be involved, but the prime importance of excessive cigarette smoking in lung cancer is hardly open to question.

*Oberling, C.: Le grave problème du cancer bronchique. [The serious problem of bronchial cancer.] Presse méd. 62: 712-715, May 5, 1954; from abstr. in J. A. M. A. 155: 1604, Aug. 28, 1954.*

### Chronic Bronchitis and Bronchial Carcinoma

Autopsy findings in a number of patients dying after long-continued chronic bronchitis and emphysema confirmed clinical opinion that death had resulted from terminal bronchopneumonia, but the striking feature was the coexistence of primary bronchogenic carcinoma that was not recognized during life. It is felt that this observation merits investigation into whether bronchogenic carcinoma is commoner in patients with long-standing chronic bronchitis and emphysema than in the rest of the population. If this is so, we should have to send chronic bronchitics to the hospital for work-up whenever exacerbations occurred, revising the teaching that the possibility of bronchogenic carcinoma must be remembered in patients more than 40 years of age with recent

pulmonary symptoms or signs. This observation may be significant in relation to the problem of tobacco and lung cancer. We know already that all inveterate smokers sooner or later develop a greater or lesser degree of chronic bronchitis. Is it not possible that this chronic bronchitis, per se, renders the smoker especially prone to lung cancer?

*Adams, A. V.: Chronic bronchitis and bronchial carcinoma. [Letters to the Editor.] Lancet 1: 147, Jan. 17, 1953.*

### Bronchogenic Carcinoma

A mass chest x-ray survey (on 70-mm. film) of some 239,000 persons, representing nearly half the population of San Diego County, California, was analyzed in relation to the mortality from bronchogenic carcinoma. The disease was correctly diagnosed in twenty persons, of whom seventeen died. Twenty-four others in whom it was not detected on survey films died of bronchogenic carcinoma in the following two years. Of the twenty cases found, sixteen were in men, all more than 54 years of age. Twenty of the twenty-four cases classified as negative were also in men, the youngest being 40 years of age. On review, films of the latter group were again found to be negative in the majority of cases, although at least six persons should have been recalled for 14×17-in. films. The average time from screening to onset of symptoms in this undetected group was nine months. As only 10 per cent of persons with bronchogenic carcinoma can be cured after onset of symptoms, it is apparent that an interval of one year between survey films is too long. Examination every six months of all men more than 40 years of age should be considered.

*Churchill, A. S.: Bronchogenic carcinoma in San Diego County: relation of mortality rates to findings in mass chest x-ray survey. California Med. 78: 232-235, March, 1953.*

### Cytology and Cancer of the Lung

At present, with current diagnostic methods, there is no substitute for cytological examination of smears of sputum

and bronchial secretions as the most important single pathological method of arriving at a correct early diagnosis of carcinoma of the lung. Correlation of the cytological procedure with examination of bronchial secretions is positive in all cases in which a bronchoscopic biopsy can be obtained and, in addition, it is positive in many more in which such tissue cannot be procured. While aspirated secretions as they appear in the bronchi give a high percentage of positive diagnoses, saline washings of the suspicious areas involved give still a higher percentage. Of a total of 540 cases of carcinoma of the lung examined cytologically, positive cytological diagnoses were made in 476 (88.3 per cent); positive bronchoscopic biopsies were obtained in 167 (30.9 per cent); and positive cytological diagnoses and completely negative bronchoscopic findings for tumor in 156 cases. In a separate series, cytology examination provided the only preoperative morphological evidence of cancer in thirty-nine (24 per cent) out of 162 proved cases of carcinoma of the lung that came to surgery. Aside from its direct aid in establishing a diagnosis, the availability of the cytological technique has been of inestimable value in increasing the clinician's awareness of the possibilities of early diagnosis in cancer of the lung.

*Herbut, P. A.: Correlation of cytological with pathological findings in tumors of the lung. In Proceedings; Symposium on Exfoliative Cytology, October 23-24, 1951. New York: American Cancer Society, Inc. [1953]; pp. 50-57; disc. Benioff, M. A.: pp. 58-60.*

### Coin Lesions of the Lung

A series of 40 consecutive coin lesions of the lung in which the diagnosis was histologically verified is reported. The following characteristics are considered definitive for this type of lesion: 1 to 5 cm. in size, round or oval in shape with sharply circumscribed borders, surrounded on all sides by normal appearing lung, producing no symptoms, homogeneous in density or containing calcium, and solitary. In the series of forty cases, surgical excision was performed on all but two after the discovery of the nodule by routine roentgen-ray examination of the

chest. Tuberculoma was the usual preoperative diagnosis. A malignant tumor was encountered in seven instances (17.5 per cent). Five cases are presented to illustrate the hazards of the watchful-waiting program sometimes advocated in cases of this type. Although it cannot be stated with statistical accuracy just how frequently these lesions cavitate and spread, it is well known that such a disaster occurs occasionally. Of much greater import is the fact that until histological study of the excised mass has been carried out, the diagnosis can only be presumptive. Experience has shown that it is not safe to manage these patients on the assumption that coin lesions are probably benign. In a collected series of 362 patients with histologically verified coin lesions, including those reported in this paper, neoplastic disease was found in 108 cases. The authors feel that a cancer rate of nearly 30 per cent makes it difficult to defend any therapeutic regimen that does not provide for their prompt removal.

*Storey, C. F.; Grant, R. A., and Rothmann, B. F.: Coin lesions of the lung. Surg., Gynec. & Obst. 97: 95-104, July, 1953.*

### Lung Tumors Induced by Urethan

Fetuses removed from pregnant mice injected five hours earlier with urethan developed more tumors per lung than offspring born naturally or than their urethanized mothers. Lung tumors developed in 82 per cent of fetuses removed from mice five minutes after injection with urethan. However, fetuses removed after a five-hour in utero exposure to the drug had more pulmonary tumors than did the parent or the mice exposed for only five minutes. Newborn mice injected with the carcinogen had fewer tumors than did fetal mice exposed for five hours but had more than the five-minute fetal group. Susceptibility to urethan apparently is not decreased by age, since injection produced a higher lung-tumor incidence in 47-day-old animals than in newborns.

*Klein, M.: Influence of urethan on lung tumorigenesis in immature, newborn, and fetal mice. [Abstr.] Proc. Am. A. Cancer Research 1 (2): 26, 1954.*

## Diagnosis of Pulmonary Metastases

A study is presented of 105 cases of authenticated pulmonary metastases comprising fifty-six female and forty-nine male patients. The preponderance of females was influenced by the incidence of breast cancer and by its tendency to metastasize to the lungs. In forty-two cases, including twenty-one cases of breast cancer, the neoplasm originated in the genitourinary system. Gastrointestinal neoplasms contributed eleven cases. Other lesions in the order of incidence were: lymphoblastoma, skin neoplasms and melanoma, soft-tissue sarcoma, and respiratory carcinoma. Nine cases were classified "miscellaneous," and in twelve cases the primary site was unknown. Diagnosis of pulmonary metastases may be impossible without biopsy, and the site of origin may be difficult to determine, even at autopsy, when tumors of highly undifferentiated cell types involve multiple organs. Chest roentgenograms give little aid in establishing the primary site; when metastases are suspected, further investigation of the most probable primary sites is indicated, the genitourinary tract and breast being especially important.

Russo, P. E., and Cavanaugh, C. J.: *Diagnosis of pulmonary metastases; a study of 105 cases. Radiology* 60: 198-201, Feb., 1953.

## The Diagnostic Value of the Papanicolaou Technique in Pulmonary Cancer

Any patient with an intractable, spasmodic cough, particularly one that produces blood-streaked sputum, should have a cytological examination of that sputum. The hacking cough of the cigarette smoker is a notorious red herring that misleads the physician into believing that it results from the irritation of the smoke rather than from the possible consequences of that irritation. As the incidence of pulmonary cancer increases, chain smokers and patients who think they have asthma should be particularly suspect. Broncho-

genic carcinoma can be detected in cytological smears before biopsies to reveal its presence are possible. While such examinations have to be made by the pathologist, the smears can be prepared by the general practitioner. Sputum is procured by asking the patient to cough deeply and to expectorate the resulting sputum directly into a bottle containing 30 cc. of 70 per cent alcohol. Bronchial aspiration or washing need only be resorted to if the sputum has been negative in spite of persistent symptoms or if the question as to which lung is involved cannot be settled by physical examination or by roentgenograms. The material collected should be smeared out evenly over glass slides after it has been coagulated by the alcohol or (in the case of bronchial sediments) centrifuged for a time. The smears are plunged immediately into a mixture of equal parts of ether and 95 per cent alcohol, which fixes and renders them transparent at the same time as it dehydrates. Staining by one of the Papanicolaou techniques is best carried out in a laboratory equipped to do such work. Pulmonary cancer can be as readily detected by exfoliative cytological methods as can carcinoma of the female organs, i.e., in about 90 per cent of the positive cases, with the type accurately identified in about 80 per cent of the cases.

Foot, N. C.: *The Papanicolaou technique; its value in the diagnosis of pulmonary cancer. Connecticut M. J.* 18: 651-653, Aug., 1954.

## Blood Groups in Lung Cancer

Cancer of the lung appears to occur independently of ABO blood-group distribution. The authors report that in a group of 777 patients with cancer, oat-cell tumors developed most often in patients with group-A blood and least often in subjects with group-O. Pulmonary neoplasms occur more frequently in Rh-positive persons.

McConnell, R. B.; Clarke, C. A., and Downton, F.: *Blood groups in carcinoma of the lung. Brit. M. J.* 2: 323-325, Aug. 7, 1954.

# Smoking and Lung Cancer: Pros and Cons

*E. Cuyler Hammond, Sc.D.*

It is generally accepted that lung cancer can be caused by a number of different agents inhaled into the lungs. Among those most frequently mentioned in this respect are dusts containing radioactive substances, chromates, or asbestos. In each instance, the major reason for believing that a causal relationship exists is the fact that workers exposed to the dust have an incidence of lung cancer far in excess of the incidence of this disease in the general population. No one has suggested any reasonable alternative explanation for the observed association between exposure to these substances and the occurrence of the disease. The fact that they come into direct contact with lung tissue lends added plausibility to the theory. The case against radioactive dusts is further strengthened by the fact that cancer can be produced experimentally by ionizing radiation.

Now, four objections might be raised to accepting this evidence as positive proof of a causal relationship. First, it might be pointed out that some workers fail to develop lung cancer after being exposed to such dust for many years. However, very few disease-producing agents of any sort cause disease in all individuals exposed to them. Individuals vary in their susceptibility to most maladies and there is no reason to believe that cancer is an exception. Indeed, experimental evidence suggests that individual susceptibility plays an extremely important role in the development of malignant neoplasms.

Second, no one has yet demonstrated the exact mechanism within a living cell by which chromate or asbestos dust causes lung cancer. There are those who would withhold judgment until all details of the reaction have been worked out. In answer, it might be said that the mechanism by which carcinogenic chemicals produce cancer in experimental animals is by no means fully understood; yet the phenomenon cannot be denied. Detailed knowledge of mechanisms is obviously desirable

but is not essential for the determination of cause-and-effect relationships.

The third objection is that proof is lacking that it is respectively a radioactive substance, a chromate, and asbestos that are the active lung-cancer-producing agents in these dusts. For example, it may be that asbestos does not cause lung cancer but that some other substance in the dust is responsible; or it may be that it is the combined effect of asbestos plus some other ingredient of the dust that is responsible. The identification of the active agent or combination of agents is of considerable scientific interest but is not necessarily of any great practical importance. Protecting workers from exposure to the dust would be effective in any event.

The fourth and final objection is that it has not been positively demonstrated experimentally that either chromates or asbestos can be used to produce cancer of any site in experimental animals. There are those who believe that causal relationships should never be considered as established without experimental verification. If this be true, then several whole fields of science (e.g., astronomy) must be considered as highly dubious because they do not lend themselves to experimental methods. Different strains of animals vary so much in their susceptibility to cancer that great caution must be used in interpreting findings from animal experiments in terms of cancer as it occurs in man. Most workers in the field consider that the epidemiological evidence linking chromate and asbestos dusts to lung cancer is so strong that conclusions can be drawn in the absence of experimental confirmation.

No one has proposed that the evidence indicating that radioactive dust is a cause of lung cancer is proof that chromate dust and asbestos dust DO NOT cause lung cancer. In other words, these are not considered to be mutually exclusive hypotheses. On the contrary, there is very strong evidence that several quite different substan-

ces can cause lung cancer and there is weaker evidence that places many other substances under suspicion. All of these are dusts, vapors, or gases. One thing at least seems to be quite certain: lung cancer can be produced in susceptible individuals by the action of certain substances inhaled into the lungs. That is to say, its occurrence cannot be attributed in every instance solely to the action of some inherited or constitutional factor. As a corollary, it follows that the elimination of the responsible environmental factors would reduce the incidence rates of the disease.

The major evidence linking cigarette smoking to lung cancer is much the same as the major evidence in respect to the inhalants just discussed. Lung-cancer-death rates are many times higher among men who are heavy cigarette smokers than among men who have never smoked. This fact has been well established by a large number of independent studies conducted in this country and abroad. All of the investigations published up to last June were conducted by the so-called historical or retrospective method. This consists in comparing the smoking histories of lung-cancer patients with the smoking histories of well persons or people with other diseases. In every such study, a much higher percentage of heavy cigarette smokers was found among the lung-cancer patients than among people in other groups. The results varied in the degree of association found, but the association was very high in all instances.

In spite of the consistency of these findings, some investigators, myself among them, thought that there was a possibility that they were misleading because of the method employed. There was a theoretical possibility of distortion owing to biasing factors either in the selection of subjects or in the taking of the histories. For this reason, we in the American Cancer Society checked the findings by a study of totally different design that avoids the principal difficulties that may arise in the use of the retrospective approach. We made use of what is known as the prospective or follow-up approach.<sup>2</sup> Between January and June of 1952, volunteer workers of the

Society obtained information as to the smoking habits of a very large number of white men between the ages of 50 and 69. These men are being traced annually. Out of 187,766 men studied, 4854 were reported as having died by October 30, 1953. Of these, 167 deaths were attributed to lung cancer according to the death certificates. Upon analysis, it was found that the lung-cancer-death rate was about nine times as high among men who were smoking a pack or more of cigarettes a day than among men who had never smoked. This ratio is highly significant statistically but should not be considered as exact because of sampling variability. More precise information will be available after a longer period of follow-up. Moderate cigarette smokers also had a considerably higher lung-cancer-death rate than men who had never smoked. There was no indication that pipe and cigar smoking are significantly associated with lung cancer, but the number of cases presently available for analysis is not sufficient to draw positive conclusions on this point. Regular cigarette smokers also had higher death rates from coronary-artery disease and from cancer of sites other than the lung than did men who had never smoked.

Doll and Hill have reported the first findings from a very similar prospective-type study made on British physicians. They also found a very much higher lung-cancer-death rate among heavy smokers than among nonsmokers.

The fact that these two prospective studies fully confirm the findings in the earlier retrospective studies proves beyond reasonable doubt that there is actually a high degree of association between smoking habits and the occurrence of lung cancer. Apparently there is now little if any dispute concerning the validity of this evidence. However, differences of opinion exist as to how it should be interpreted.

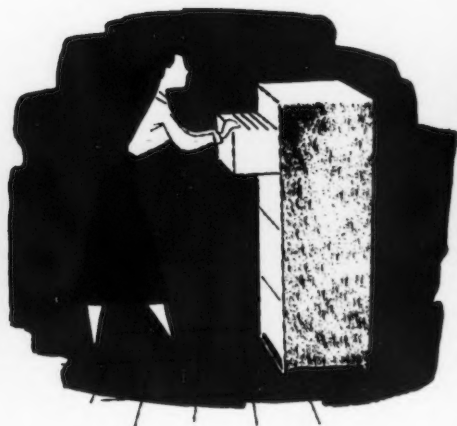
The high degree of association between heavy cigarette smoking and the occurrence of lung cancer must have some rational explanation. The simplest and most obvious hypothesis is that cigarette smok-

*Text continues on page 92.*

# Mechanics of ACS Follow-up Study



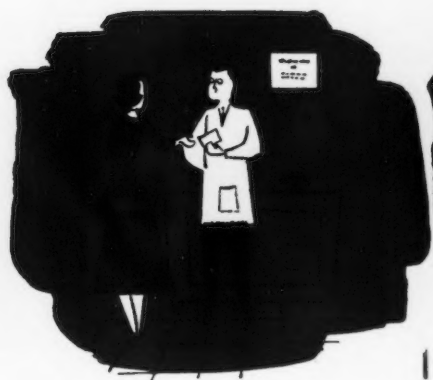
More than 22,000 volunteers give questionnaire on smoking habits to more than 200,000 men aged 50 to 69 years.



Follow-up forms are prepared and filed in ACS Division office.



Search for death certificate in state Bureau of Vital Statistics.



When "cancer" appears on death certificate, diagnosis is verified by certifying physician.

# Study on Smoking



Original questionnaires are sent to Statistical Research Section, ACS National Office.



Follow-ups in November 1952, 1953, and 1954. Volunteer notes when he last to follow.



Photostatic copies or abstracts of death certificates are analyzed in Statistical Research Section, ACS National Office.



First report based on 187,766 men with 4854 deaths to October 31, 1953, published in J. A. M. A. 155: 1316-1328, Aug. 7, 1954.

ing, by some mechanism, increases the probability that an individual will eventually develop lung cancer. In everyday language, this would mean that cigarette smoking is a cause of lung cancer, although not the only cause. It does not necessarily imply that cigarette smoking alone can cause lung cancer. For example, the observed association might be produced if lung cancer were caused by a combination of cigarette smoking plus certain other extrinsic and/or intrinsic factors.

The four objections discussed in relation to radioactive, chromate, and asbestos dusts have been raised against the hypothesis that cigarette smoking is a causative factor in lung cancer. For reasons already mentioned, I do not believe that they carry much weight.

The objection most frequently raised is the inadequacy of experimental evidence bearing on the problem. While it is uncertain whether chromates and asbestos can produce cancer of any site in experimental animals, it has at least been demonstrated that cigarette-smoke condensate can produce skin cancer when applied to mice of a certain strain.<sup>3</sup> The investigators who reported this finding do not think that it adds much to the evidence for a casual relationship between smoking and lung cancer in human beings. Their reason: what will produce cancer in one tissue of a particular species of animal will not necessarily produce cancer in another species or in a different tissue of the same species. The same reasoning will apply when and if anyone finally succeeds in producing lung cancer experimentally in an animal by the inhalation of tobacco smoke. Now, this is a knife that cuts both ways. If animal experiments are considered to yield valid evidence as applied to cancer in man, then the work of Wynder, Graham, and Croninger gives strong added support to the hypothesis that smoking is a causative factor for cancer in man. On the other hand, if it is considered dangerous to interpret animal experimental data as applying to cancer in man, then the present lack of more definitive experimental evidence is unimportant

in relation to the hypothesis under discussion.

There has been much discussion of the fact that lung cancer is far less common in women than in men and that the death rates from this disease have not shown such a rapid increase in women as in men. The reasons for this are not clear and it may be that it reflects a sex difference in susceptibility. Be that as it may, among people more than 50 (at which age lung-cancer-death rates begin to mount) a much smaller proportion of women than men have a long history of heavy cigarette smoking. While this is not very strong evidence one way or the other, it is at least consistent with the hypothesis that cigarette smoking is a causative factor in the development of lung cancer. On the other hand, the sex difference casts some slight doubt on the hypothesis that general air pollution in cities (to which both sexes are exposed) is an important causative factor in lung cancer.

The concurrent rise in lung-cancer-death rates and the per capita sale of cigarettes is consistent with the hypothesis regarding smoking. The importance of this evidence lies in the fact that had the trends run in opposite directions, then it would have done much to disprove the hypothesis of an important causal relationship between smoking and lung cancer. However, many of the other suspected causes of lung cancer also increased during the same period of time.

Some investigators have made much of the fact that the per capita consumption of cigarettes is lower in Great Britain than in the United States, yet the lung-cancer-death rate is higher in Great Britain than in the United States. However, up to 1941, the per capita sale of cigarettes was higher in Great Britain than in the United States. This could account for the difference in lung-cancer-death rates if there is a long latent period between critical exposure and the clinical manifestations of the disease. Other possible explanations that have been suggested are: (1) it is said that British people smoke more of each cigarette than do wasteful Americans and therefore get a higher dose

of nicotine and tar; and (2) different tobacco blends are used for cigarettes in the two countries. Perhaps other environmental factors account for all or part of the difference in lung-cancer-death rates. Whatever the explanation of the difference, the fact remains that there is a high degree of association between smoking habits and lung-cancer-death rates in both countries.

According to official reports, lung-cancer-death rates are higher in urban areas than in rural areas. This may be an indication that general air pollution is an important factor in the development of lung cancer. However, there is also evidence that the per capita consumption of cigarettes tends to be higher in urban areas than in rural areas. Thus the difference in urban and rural death rates is consistent with both hypotheses—and both may have merit.

A few authors have expressed the opinion that the rise in lung-cancer-death rates has resulted from the rise in a host of different environmental factors, mostly air pollutants of one sort or another. From this they have reasoned that cigarette smoking is either unrelated to lung cancer or only plays a minor role. This argument has no validity unless the major premise can be established; and there is no proof at present. Furthermore, this would leave unexplained the association between cigarette smoking and lung cancer.

The fact that cigar and pipe smoking seem to be either not associated with lung cancer or associated to a much less degree than cigarette smoking is somewhat puzzling. There is still some doubt as to the degree of this difference. Several explanations have been suggested, which may or may not be correct: (1) there is an impression that cigar and pipe smokers tend to inhale less than cigarette smokers; (2) much of the nicotine and tar condenses in the stem of a pipe and the butt end of a cigar; (3) cigar tobacco is very different from cigarette tobacco and pipe tobacco is somewhat different from cigarette tobacco; and (4) the combustion products in cigarette smoke may be quite different from the combustion products in cigar

and pipe smoke because of difference in the rate of burning, cigarette paper, additives used in cigarettes, etc.

Now suppose that cigarette smoking is not in any sense a causative factor in the development of lung cancer. How then could the high association between cigarette smoking and lung cancer be explained?

Broadly speaking, there is only one alternative hypothesis. It might be that heavy cigarette smoking is associated with one or more factors that are the actual causes of lung cancer. These factors could be either extrinsic (environmental) or intrinsic (hereditary or constitutional).

There is only one widespread environmental factor now under strong suspicion as having an influence on the development of lung cancer that is also probably associated to some degree with smoking habits in the general population. Both air pollution and the per capita consumption of cigarettes are higher in urban areas than in rural areas. Thus, if the entire population of the United States were studied, it is likely that cigarette smoking would be found to be at least slightly associated with exposure to general air pollutants. It is possible that the higher lung-cancer-death rate in urban areas than in rural areas is attributable to the combined action of these two factors. However, when the two populations are studied separately, an association is still found between cigarette smoking and lung-cancer-death rates. Thus even if both of these factors are important, the association between them would only account for a small portion of the association between smoking and lung cancer.

It has been suggested that some factor in modern living, such as psychological stresses or pressure of work leads to both lung cancer and a tendency to heavy cigarette smoking. This is an interesting speculation, but there is very little evidence at the present time to support it. While there is reason to suppose that such stresses lead to heavy cigarette smoking there is no evidence whatsoever that they lead independently to a ninefold increase in lung-cancer-death rates. Of course,

stress might lead indirectly to lung cancer by causing heavy cigarette smoking, which in turn might cause a higher incidence of the disease. Stress, by affecting glandular activity, might also perhaps increase (or decrease) susceptibility to cancer in general and have an additive effect, such as was discussed in relation to cigarette smoking and air pollutants.

Another possibility is that some inherited or constitutional factor produces both a tendency to smoke cigarettes and a tendency to develop lung cancer.

There being a virtually unlimited number of extrinsic and intrinsic factors operating on the human population, there is unlimited opportunity for speculation of this kind. Such speculation is useful for developing hypotheses as a basis for research. However, it cannot be taken seriously until reasonable evidence is produced (1) that the factor(s) in question is very highly associated with lung-cancer-incidence rates, (2) that it is also very highly associated with cigarette smoking, and (3) that these two associations hold true in the general population. No such evidence has been presented up to the present time.

### Summary and Conclusions

1. It has been shown that a high association exists between cigarette smoking and the incidence of lung cancer.

2. This association might be explained by either one of two alternative hypotheses:

(1) Cigarette smoking increases the probability that lung cancer will develop; that is, it acts as a causative factor.

(2) Cigarette smoking does not increase the probability that lung cancer will develop; but cigarette smoking is highly associated with some factor or factors that do cause lung cancer.

3. The following may be said of the first of these hypotheses: It has not been conclusively demonstrated by experimentation; but it is doubtful if anything short of human experimentation could

produce evidence that would be universally accepted as absolutely conclusive. All other evidence bearing on the problem is consistent with this hypothesis. No evidence has been produced that strongly contradicts this hypothesis.

4. The following may be said of the second, or alternative hypothesis: A few factors (stress, heredity, etc.) have been suggested that might possibly produce a high incidence of lung cancer and at the same time be independently associated with heavy cigarette smoking. Evidence is lacking to support any one of the possibilities so far proposed. Such evidence may be developed by future research. Some factor or factors at present not under suspicion may perhaps act in this way; but this is unknown.

5. In my opinion, the first hypothesis is reasonable. It is supported by the fact that it is consistent with many bits of evidence no one of which is in itself conclusive. While the only alternative hypothesis that has been proposed is possible, it is a speculation virtually unsupported by any evidence now in hand. Until such time as strongly contradicting evidence is developed or the alternative hypothesis is proved, I believe that it is reasonable to subscribe to the theory that cigarette smoking increases the probability that lung cancer will develop.

6. Cigarette smoking is certainly not the only cause of lung cancer. In my opinion, at the present time it is not possible to make an exact estimate of the proportion of lung-cancer cases in which cigarette smoking played a causative role. However, considering all information at present available, it appears to me that cigarette smoking is an extremely important factor.

### References

1. Doll, R., and Hill, A. B.: *The mortality of doctors in relation to their smoking habits; a preliminary report*. Brit. M. J. 1: 1451-1455, 1954.
2. Hammond, E. C., and Horn, D.: *The relationship between human smoking habits and death rates; a follow-up study of 187,766 men*. J. A. M. A. 155: 1316-1328, 1954.
3. Wynder, E. L., Graham, E. A., and Croninger, A. B.: *Experimental production of carcinoma with cigarette tar*. Cancer Research 13: 855-864, Figs. 1-20, 1953.

# Lung Cancers and Their Causes

*W. C. Hueper, M.D.*

The recent forceful propagation of the cigarette theory of lung cancer has greatly stimulated interest in the causes of these tumors. The present controversy related to the etiology of pulmonary cancers is not so much concerned with the question whether or not cigarette smoking may cause cancer of the lung as with the determination of the relative role that cigarette smoking in relation to the other known and still unknown environmental factors may assume in the production of these neoplasms and in their increase during recent decades. Since it has been claimed on the basis of restricted statistical and experimental evidence that cigarette smoking is the principal cause of lung cancer and has been mainly responsible for its marked and progressive increase, a critical evaluation of the evidence available that does not support this contention and that indicates that other environmental factors play a more important part may be in order so as to obtain a balanced assessment of the causal aspects of the lung cancer problem.

## **Defects in the Evidence Supporting the Cigarette Theory of Lung Cancer**

Although the statistical data collected by the majority of investigators have shown the existence of positive and allegedly causal associations between cigarette smoking and lung cancer, the following observations militate against the claim of a predominant role of cigarette smoking.

1. Several recent statistical analyses failed to confirm any consistent correlation between cigarette smoking and lung cancer.

2. The liability to error in correlating conditions that are very common, such as

lung cancer, cigarette smoking, pulmonary tuberculosis, exposure to silica, arsenicals, soot, and engine exhaust, may be considerable, since such common conditions must often be concomitant without implying a causal relationship, unless additional epidemiological, medical, and experimental evidence supports such a conclusion. The coincidental nature of such statistical correlations is, for instance, well established for exposure to silica and pulmonary cancer and for the frequent co-existence of pulmonary tuberculosis and lung cancer. Similarly fallacious from a scientific-medical viewpoint is the repeatedly expressed contention that trauma to the breast is a significant causal factor in the development of cancer of this organ because of the existence of significant statistical relations between the two events.

3. A distinct increase in lung cancer started around the turn of the century, i.e., well before the cigarette-smoking habit became widespread and two decades before even the minimal latent period of any large number of potential cigarette-smoke cancers of the lung had elapsed.

4. This increase in frequency of lung cancer was, moreover, not a uniform phenomenon but was first observed in some highly industrialized regions and communities mainly located in Central Europe. It extended from such foci in irregular fashion to other areas and countries during the following decades, becoming demonstrable in the Scandinavian countries and Italy only after 1930 and involving rural population groups of the same country much later and to a lower degree than urban populations. Lung-cancer rates have preserved this irregular epidemiological pattern into present times. The highest rates are in general found in large, industrialized communities. They drop gradually with the size of the community and the density of population to the lowest rates present in the rural, agricultural areas. However, even here

From the National Cancer Institute, National Institutes of Health, United States Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland.

marked variations exist in the lung-cancer rates observed among metropolitan areas of the same country (U.S.A.) and even the same State (Ohio). It is, moreover, remarkable that the annual progression rates of lung-cancer deaths in the U.S.A. were higher during the first three decades of this century than during the subsequent fifteen years and that the progression rates of lung-cancer morbidity in the populations of ten metropolitan areas in the United States are highly irregular according to the results of surveys made in 1937 and 1947.

Such local variations in lung-cancer frequency ranging up to several hundred per cent, as well as the graduated incidence pattern in urban-rural respects, are not in harmony with the concept that one single habit factor has been operative in the production of lung cancer. Rather these observations indicate that several or many factors acting in different intensity and combinations and at different times have been active in bringing about this highly characteristic and significant epidemiological pattern, which conforms well with the occupational and environmental air-pollution pattern related to the development, spread, and types of modern industry through the various countries, regions, and towns.

Such marked fluctuations in lung-cancer frequency of regional and particularly rural-urban type can not conveniently be disposed of by the explanation that they reflect differences in the cigarette-smoking habits of different population groups. There is likewise no acceptable scientific evidence supporting the claim that the paradoxical behavior of the progression rates of lung cancer during the last four decades is attributable to the fact that many cigarette smokers did not live long enough in recent decades to develop lung cancer because of their precocious death from coronary thrombosis—also allegedly elicited in the majority of cases by cigarette smoking.

5. It is remarkable, moreover, that there does not exist any parallelism between the rate of cigarette consumption per capita and the lung-cancer-death

rates of different countries. The lung-cancer-death rate in England, for instance, is twice as high as that in the United States although Americans smoke 30 per cent more cigarettes than Englishmen. Such discrepancies cannot intelligently be explained by the bold assertion that Englishmen smoke cigarettes, for economical reasons, to their very tip and therefore inhale more tar fumes than Americans who often throw cigarettes away when half smoked.

6. In view of the considerable variations in the male-female sex ratio at different times, in different localities, and in different demographic groups ranging even during recent years from 1:1 to 50:1, it is most unlikely that such discrepancies and changes are attributable to variations in the intensity of one single factor such as cigarette smoking. They appear rather to be due to alterations and variations in the type and extent of action of a broad spectrum of environmental carcinogenic agents affecting the members of the two sexes to different degrees.

7. The various known or suspected lung-cancer-causing agents or exposure conditions encountered in industry have been shown to be associated with the development of pulmonary cancers of different histological types. In fact, two different histological types, such as squamous-cell carcinoma and adenocarcinoma, were occasionally found to coexist in the same pulmonary cancer. Squamous-cell carcinoma of the bronchi, therefore, is neither pathognomonic for any specific respiratory carcinogen nor is it the only histological type found in lung cancers of occupational origin. Long before the cigarette era squamous-cell carcinomas of the bronchi represented an appreciable fraction of the total lung cancers observed. They are not pathognomonic of a cigarette-smoke etiology. Therefore it is scientifically incorrect to claim that this histological type of cancer was rare before 1920 and appeared only with the adoption of the cigarette-smoking habit.

8. It is definitely surprising that there does not exist a positive statistical correlation between cigarette smoking and

cancers of the lip and mouth, although without doubt tarry liquid oozing from the tip and tarry fumes have direct and intense contact with these parts, since statistical evidence supports the claim that cigar and pipe smoking conveys an excessive liability to labial and oral cancer. One must wonder also about the total absence of cancer of the skin of the fingers holding cigarettes in view of their often intensely dark-brown-stained skin impregnated with tobacco tar. The assertion that the first three fingers are immune to tobacco tar, while they are not immune to coal tar, is an evasive explanation lacking any scientific value and manufactured ad hoc.

9. The claimed absence of a positive statistical association between lung cancer and the habit of inhaling cigarette smoke is inconsistent with the rule that the incidence rate of occupational cancers increases with the intensity of exposure to a carcinogen. It is also disconcerting to note that there is no significant statistical relation between chronic tracheal and bronchial diseases and cancer of the lung, although cigarette cough is a characteristic symptom of chain smokers and despite the fact that such respiratory diseases are excessive in several worker groups suffering from certain types of occupational lung cancer.

10. Although, after many failures to demonstrate known carcinogenic hydrocarbons in cigarette tar and cigarette-paper tar, English investigators recently succeeded in obtaining very small amounts of 3,4-benzpyrene from artificially smoked cigarettes, it should be noted that this polycyclic hydrocarbon can be obtained during the incomplete combustion of any carbonaceous matter under suitable conditions of temperature and oxygen supply.

11. The inconsistent results obtained by various investigators when tobacco or cigarette tar was applied to the skin of, or inhaled by, experimental animals indicate that tobacco tar is apparently at best a weak carcinogen to the skin of mice and perhaps also to the skin of rabbits, while the inhalation of cigarette smoke even when successful failed to elicit lung tu-

mors in mice that are histological and histogenetic equivalents of the human bronchogenic variety of cancer.

The development of pulmonary tumors observed in certain strains of inbred mice, moreover, depends upon the action of a primary hereditary factor that, according to our present knowledge, is totally absent in the causation of the great majority of bronchogenic cancers in man. Constitutional hereditary, congenital, or acquired factors may influence cancer development in man by their possible effects upon susceptibility to exogenous or endogenous specific agents but they are not truly causative in their action.

It is evident from this critical analysis of the evidence related to the cigarette theory of lung cancer that it contains a number of serious defects and inconsistencies and that for these reasons alone an acceptance of the broad claims made for it should be withheld.

#### **Etiological Importance of Environmental Factors of Nontobacco Nature**

The wisdom of this just-stated conclusion becomes strikingly obvious when due consideration is given to the large amount of data incriminating other environmental air pollutants with which, for occupational and environmental reasons, industrial worker groups as well as the general population have effective, frequent, and prolonged contact.

It is often asserted by the protagonists of the cigarette theory that there does not exist any alternative theory of general validity that might account for the causation of most lung cancers and that would explain the increase in lung cancer and its sex distribution. The facts are as follows:

1. The evidence on specific occupational lung-cancer hazards affecting almost exclusively males in restricted worker groups provides in many respects conclusive proof of the existence of carcinogenic air pollutants.

2. The available information indicates that similar or identical, while often miti-

gated, exposures exist not only for much larger groups of industrial workers composed of several millions of persons but also for the general population through the medium of industrial effluents, gasoline and diesel engine exhaust, and dusts from asphalted and oiled roads and abraded rubber tires.

3. The epidemiological evidence incriminating exposures from these sources in the production of lung cancer and its increased frequency among large industrial worker groups and the general population is almost as good as that available for cigarette smoking.

4. The experimental evidence in regard to the carcinogenic action and potency of these industrial and industry-related factors, especially as far as coal tar and atmospheric soot and other carbonaceous and metallic pollutants are concerned, is a great deal more conclusive than that supporting carcinogenic properties of tobacco tar and strikingly demonstrates their far-greater carcinogenic potency over that experimentally displayed by tobacco tar.

The existence of respiratory-cancer hazards involving the lung and/or the nasal cavity, paranasal sinuses, and larynx has reliably been demonstrated for:

(1) retort workers of gas-manufacturing plants and coke ovens because of the inhalation of hot coal-tar fumes;

(2) workers exposed to the inhalation of certain petroleum-oil mists and fogs encountered in some operations of oil refineries, in metallurgical manufacturing plants, and textile works;

(3) isopropyl-alcohol manufacturers exposed to inhalation of vapors from the crude liquor (isopropyl oil);

(4) nickel refinery workers having contact with nickel dust and nickel carbonyl vapors;

(5) chromate manufacturers and chrome-pigment handlers inhaling chromium-containing compounds;

(6) arsenical insecticide producers and users;

(7) asbestos workers with pulmonary asbestosis;

(8) radioactive-ore miners and lumi-

nous-dial painters inhaling radioactive dust and/or gases.

The lung-cancer-attack rates for members of these occupational groups are many times those found for the general population of the same age and sex. Females were affected by occupational respiratory cancers through contact with only two of the agents listed (asbestos—lung; radioactive gases [luminous-dial painters]—paranasal sinus) because males are exclusively employed in the other hazardous operations. Whenever in a hazardous industry, such as the asbestos industry, both males and females were employed and sustained the same type and a similar degree of exposure, there was a trend toward an equalization of the lung-cancer-attack rate.

Exposures to occupational respiratory carcinogens are sometimes characterized by a typical symptom complex involving not only the respiratory organs but also other tissues and organ systems. The symptom complex associated with coal-tar cancer provides a striking illustration of this diagnostically and etiologically important phenomenon. Respiratory exposure to coal-tar fumes always entails also cutaneous contact with this material and accounts for the occurrence of the various manifestations of chronic coal-tar dermatitis: warts, cutaneous horns, papillomas, and carcinomas of the skin among members of such worker groups. Such a characteristic cutaneous symptom complex is, on the other hand, totally absent for cigarette chain smokers, while the chronic inflammatory manifestations of laryngitis and tracheitis seen in chain smokers still have a debatable significance. Cancers of the trachea are uncommon and cancers of the larynx have not only shown a minor increase during recent decades but also displayed a sex-related distribution pattern different from that of lung cancers. They are, according to English statistics, more common among females in rural areas than among those residing in Greater London.

Epidemiological studies on lung cancer for larger industrial groups have demonstrated not only marked differences

of lung cancer frequency among members of various groups but also have shown excessive frequency rates for industrial populations exposed to known occupational respiratory carcinogens, such as coal-tar and pitch fumes and dust; mist, fumes, and vapors of various petroleum derivatives; metal dusts; and fumes and exhaust fumes from gasoline and diesel engines. Excessive liabilities to lung cancer have been recorded for transportation workers, rubber and plastic workers, employees of the nonferrous-metal industry, operating railroad workers, boiler scalers, metal grinders, polishers, welders, lathe workers, foundry workers, engineers, mechanics, machinists, crane operators in smelters, painters, coal-tar workers, asphalters, chimney sweeps, stokers, patent-fuel workers, furnace men, rollers, and asphalters. While the epidemiological evidence supporting such correlations between certain occupational activities and lung cancer has only circumstantial value, the observations are in good agreement with those made in connection with the recognized occupational respiratory cancers of the lung, as well as in harmony with the fact that lung-cancer rates have been found to be up to several hundred per cent higher in industrial states than in agricultural states, and in industrialized communities than in rural areas of the same state (Connecticut, New York, Ohio, Colorado, Montana) or the same country (England, Germany, Austria).

Their apparent etiological significance is, moreover, indicated by the fact that appreciable amounts of 3,4-benzpyrene have been demonstrated not only in the particulate phase of the air pollutants of the mainly coal-burning industrial cities of England but also in that of the atmosphere of Los Angeles where industry and transportation depend upon petroleum fuels.

It is moreover noteworthy that during smog conditions the benzpyrene content of the air may rise severalfold, and that in Austria the lung-cancer rate was about twice as high in communities located on main traffic arteries as in those situated remote from main highways. These ob-

servations suggest that industry-related air pollutants may represent a distinct lung-cancer hazard for considerable portions of the general population, especially those residing and working in industrialized urban communities. This conclusion is supported by the fact that during recent decades the rise in lung-cancer frequency was not only associated with an increased consumption of cigarettes, but by a remarkable, and in part even more pronounced, rise in the construction of asphalted roads, in the consumption of motor fuel, and in the production of industrial and domestic fuel oils, patent fuel, crude petroleum, petroleum asphalt, coal tar, isopropanol, asbestos, arsenic and chromium compounds, and nickel; i.e., of conditions and materials having proved or suspected relations to respiratory cancers.

In contrast to the inconsistent and controversial observations on the experimental production of cancers by tobacco tar, there is available a large array of observations on the appearance of cancers in various organs and tissues and different species following the cutaneous, subcutaneous, intrapulmonary, intraosseous, respiratory, and intravenous administration of coal tar, pitch and asphalt, soot, creosote oil, anthracene oil, shale oils, petroleum derivatives and carbon blacks and their benzolic extracts. Early and frequent cancers of the skin or subcutaneous tissue have consistently been obtained with benzol extracts of the particulate phase of air pollutants even in a strain of mice that naturally is rather resistant to spontaneous and experimental cancer formation. Considerable amounts of 3,4-benzpyrene, surpassing many times those tentatively found in cigarette tar, have been isolated from coal tar, shale oil, and soot.

Since practically all known or suspected environmental causes of lung cancer were discovered during the last twenty-five years, it is most likely that there exist other, still unknown, respiratory carcinogens. Appreciable experimental evidence, as well as a few observations on environmental lung cancer, suggests that the development of pulmonary cancers may not be entirely attributable to agents that are

inhaled, but perhaps also may be to agents entering the human body by other routes (alimentary-tract, skin, parenteral).

### Conclusions

1. The total epidemiological, clinical, pathological, and experimental evidence on hand clearly indicates that not a single but several if not numerous industrial or industry-related atmospheric pollutants are to a great part responsible for the causation of lung cancer.

2. While the available data do not permit any definite statement as to the relative importance of the various recognized respiratory carcinogens in the production of lung cancers in the general population, they nevertheless unmistakably suggest

that cigarette smoking is not a major factor in the causation of lung cancer nor had it a predominant role in the remarkable increase of these tumors during recent decades.

3. In view of the fact that not only a great deal of the existing circumstantial epidemiological evidence but also practically the entire factual and conclusive evidence available on exogenous respiratory carcinogens are either of occupational origin or point to industry-related factors, it would be most unwise at this time to base future preventive measures of lung-cancer hazards mainly on the cigarette theory and to concentrate the immediate epidemiological and experimental efforts on this evidently overpropagandized and insufficiently documented concept.

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### What's That Again?

In the busy search for other-than-cigarette-smoke causes of lung cancer two odd ones were suggested at a recent smoke-cancer-heart conference:

1. Absence from our modern, ultrahygienic, highly public-healthed environment of some unidentified, previously existing, anti-cancer, protective agent—a microorganism annihilated by sulfonamides or antibiotics, a food constituent removed by refining processes, or some other entirely unknown, eliminated environmental factor or custom of civilization.

2. Drugs, like Fowler's solution, formerly much esteemed by the physician. This idea was said to be consistent with the known long latent period of lung cancer.

These two nebulous, hypothetical factors—one negative, the other iatrogenic—show imagination but they seem, at this point, to have a good deal less to support them than cigarette smoke and dirty air of cities.



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## Clinical History

A 75-year-old man was admitted to the Clinical Center with a history of progressively increasing cough, periods of confusion, and loss of weight of one month's duration.

He was in good health until six to eight weeks before, when he began to have a nonproductive cough. Mucoïd sputum tinged with blood appeared some three weeks later. He lost about 20 lb. in weight and was noted to have episodes of disorientation, confusion, and sensory impairment of the left hand.

The patient had smoked one to two packages of cigarettes a day for forty years. During the past two years, he consumed a pint of whiskey per week and, more recently, two to four pints per week. Three years previously he had an episode of pneumonia that was treated at home with penicillin, with complete clinical recovery.

Physical examination revealed a feeble, wasted man. He coughed intermittently,

raising blood-tinged sputum, and was in obvious respiratory distress. There was a single, hard lymph node in the left axilla. He had a funnel-chest deformity and an emphysematous limitation to chest motions. He had bilateral inguinal hernias, and the prostate was irregular and of firm consistency, although not enlarged. Coordination was poor, particularly in the upper extremities, but no localizing neurological abnormalities were present. There were no other findings of significance.

A roentgenogram of the chest (Fig. 1) showed an area of infiltration or partial atelectasis involving the left lingula and left upper lobe. Examination of the sputum for neoplastic cells was negative on three occasions; two other specimens contained a few atypical cells with nuclear features suggestive of malignancy (Class III, Papanicolaou classification).

Bronchoscopy failed to reveal bronchial lesions or obstructions. Biopsy of the left axillary lymph node showed it to contain poorly differentiated adenocarcinoma.

The patient's course in the hospital was characterized by progressive respiratory difficulty, with increased respiratory rate, dyspnea, and cyanosis. The temperature during the first week did not rise above 37.9°C. He developed evidence of pneumonitis in the right upper lobe of the

Summarized discussion of Case No. Clinical Center 00-07-38, Autopsy A 53-10, at conference January 18, 1955, by Harold L. Stewart (presiding), Michael B. Shinkin (symptomatology correlations), John H. Edgcomb (history and pathology), Albert W. Hilberg (diagnostic cytology), and George L. Fite (pathology of prostate).



Fig. 1. See text.

lung, and sputum cultures recovered *Klebsiella pneumoniae*. He was treated symptomatically and with antibiotics but became steadily worse and died on the sixteenth day of hospitalization.

### Differential Diagnosis

The presumptive diagnosis of this patient even before admission to the Clinical Center was bronchogenic carcinoma. The complete clinical investigation, however, failed to make this more than the most likely presumption. It was established, of course, that he had metastatic anaplastic adenocarcinoma in an axillary lymph node. A roentgenogram of the chest showed an area of infiltration or partial atelectasis of the left lingula and left lower lobe. Abnormal cells in the sputum were present on two occasions, but in neither instance was a definitive diagnosis of malignant cells possible. It must be remembered that metastatic carcinoma of the lung also yields positive sputum smears in an appreciable percentage of the cases. Farber, for example, recorded positive smears in twenty-three of eighty-eight cases of metastatic neoplasms of the lung, as compared with 60 per cent in primary carcinoma of the lung.

The equivocal evidence on five smears in this patient was even further depreciated by the lack of positive bronchoscopic evidence of a bronchial lesion.

Thus, all that could be accepted as established was the presence of metastatic carcinoma from an unknown primary site.

Two features regarding the clinical course are worthy of comment. The first is the disorientation and mental deterioration of the patient. The neurological consultant's impression was that the patient had an organic mental syndrome with suggestive right-sided cerebral and mesencephalic signs. The most likely etiology was considered to be bronchogenic carcinoma, with multiple metastases to the brain.

The other feature of interest was respiratory difficulty and cyanosis in excess of the physical or roentgenographic findings. The patient had severe arteriosclerosis, pulmonary emphysema, and some pneumonitis, with an eventual recovery of *Klebsiella pneumoniae*. Clinically, it was considered that he had marked pulmonary fibrosis, and tuberculosis and bronchiectasis were also mentioned as possible complicating features.

In regard to the presumptive diagnosis of bronchogenic carcinoma, the history of heavy smoking of cigarettes for forty years and the history of pneumonia three years before were considered as possible evidence. However, cigarette smoking is statistically related to epidermoid carcinoma of the lung, whereas the patient's neoplasm, at least in the axillary lymph node, was shown to be an adenocarcinoma. The history of pneumonia three years before probably represented some nonspecific pulmonary incident in a 72-year-old man and could be connected with his fatal illness only most tenuously.

The clinical diagnosis was: (1) metastatic carcinoma, primary site unknown, (2) bronchopneumonia, and (3) generalized arteriosclerosis.

### Pathology

Autopsy revealed a nodular mass, about

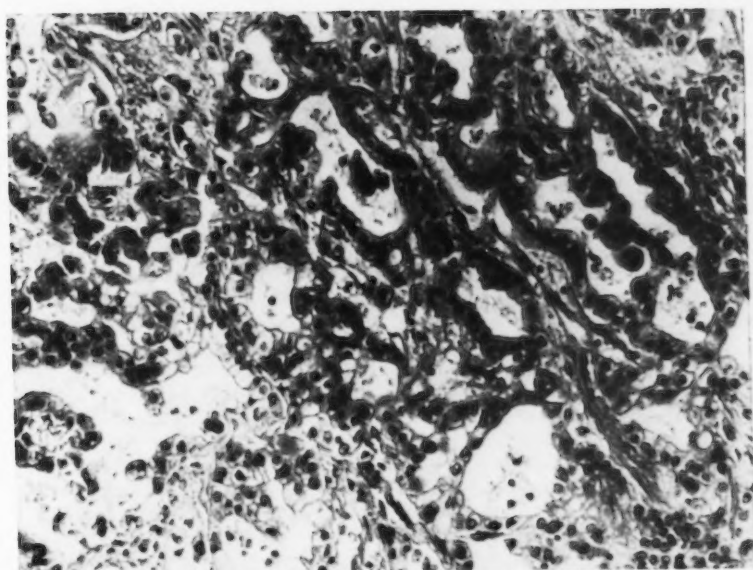


Fig. 2. Adenocarcinoma of the lung. ( $\times 180$ .)

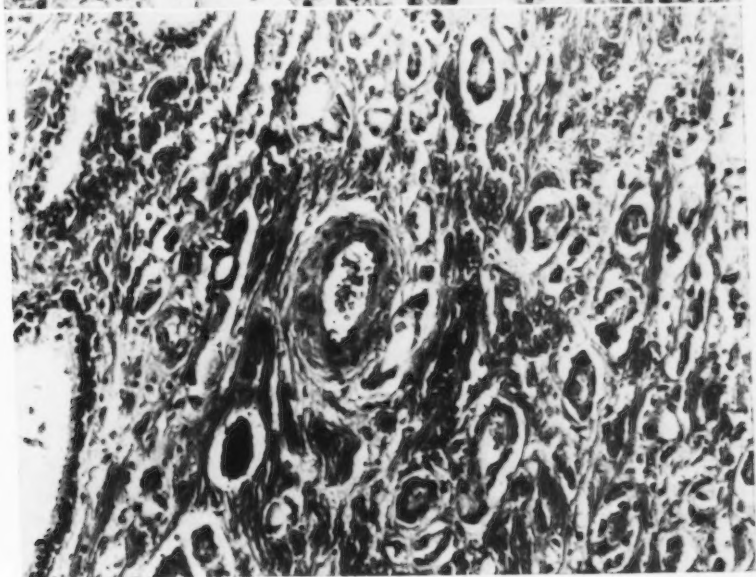


Fig. 3. Adenocarcinoma of the prostate. ( $\times 180$ .)

4 cm. in diameter, in the terminal portions of the lingula of the left lung, and a 2-cm. endobronchial lesion in the left bronchus leading to the lingula. Much of the lung tissue was traversed by firm thin trabeculae. The bronchial and lingular masses were composed of adenocarcinoma (Fig. 2) that could not be distinguished from each other. The tumor filled the lymphatics of the lung, perivascularly as well as septally, and there was also intravascular spread of the tumor.

Metastases of the adenocarcinoma were present in the hilar, anterior mediastinal, left supraclavicular, and paratracheal lymph nodes and in both adrenals. There were no metastases in the brain.

The prostate contained a small nodule of unquestionable adenocarcinoma (Fig. 3). The posterior border of the gland, the lymphatics, and the perineural spaces were free of tumor.

Additional autopsy findings included bronchopneumonia, mild pulmonary fibrosis and emphysema, generalized arteriosclerosis, and thrombosis of the right middle cerebral artery with recent encephalomalacia.

### Clinicopathological Correlation

The histological similarity between the two pulmonary tumors and the prostatic

neoplasm raises the possibility that the former could be metastases of the prostatic tumor. The prostatic carcinoma was limited to the organ and showed no intravascular, lymphatic, or perineural invasion. Evidence is, therefore, against the spread of this tumor. As Rich and Moore showed, 10 to 20 per cent of elderly males would be expected to have foci of carcinoma in the prostatic gland.

There were two distinct tumors in the left lung, as well as extensive spread of the tumor within the lung and to distant lymph nodes and to the adrenals. It is considered most probable that the bronchial adenocarcinoma arose initially and that the lingular mass represented a large metastasis in the lung supplied by that bronchus.

The patient's pulmonary difficulties are well explained by the diffuse involvement of the pulmonary blood vessels and lymphatics by the tumor, in addition to emphysema and bronchopneumonia. Such lymphangitic dissemination is well to consider in patients with cancer who have greater pulmonary difficulties than roentgenological or physical findings would explain. The central-nervous-system symptomatology, however, was ascribable to vascular occlusion on an arteriosclerotic basis, and was not demonstrated to be related to the pulmonary neoplasm.

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### New Lung-Cancer Film

*Lung Cancer: The Problem of Early Diagnosis*, a professional film, was recently produced by the American Cancer Society and the National Cancer Institute. The rapidly increasing incidence and the importance of periodic chest films are emphasized, and the several diagnostic procedures are vividly portrayed—roentgenography, exfoliative cytology, bronchoscopy, exploratory thoracotomy, and biopsy.

The film is narrated by Dr. Cameron of A.C.S. and includes comments by Dr. Ochsner of Tulane, Dr. Graham of Washington University, and Dr. Overholt of Tufts.

This 16-mm., color, sound, 28-minute film may be obtained through A.C.S. Divisions for showing to professional groups—county and state medical societies, hospital staffs, medical students, and nurses.



## DOORS' DILEMMAS

**Q** *A 57-year-old woman has been treated elsewhere for "eczema" of the right nipple for six months by means of various salves. On examination I find that the nipple is scaly and encrusted. There are no enlarged axillary lymph nodes. However, I question the diagnosis of true eczema in this patient.*

**A** This patient may have Paget's disease. She should be taken to the operating room and a wedge biopsy of the involved nipple performed for diagnosis by frozen section if possible. If a diagnosis of Paget's disease is confirmed, it is almost certain that there is an underlying infiltrating duct carcinoma, and the operative procedure then should be a radical mastectomy.

**Q** *I have a patient who has finally been proved to have cancer of the kidney. Throughout the past six months, the white-cell count has ranged more than 30,000 with 80 per cent polymorphonuclears. The bone marrow shows hyperplasia of leukocytoid elements. This patient has no evidence of infection or fever, and I am wondering whether he might also have leukemia.*

**A** Leukemoid reactions, with white-cell counts greater than 50,000 are not uncommon in cancer with early invasion of bone marrow. Cancer of the kidney has a predilection to metastasize to bone marrow. For this reason it would seem this patient has a leukemoid reaction

rather than true leukemia. Repeated careful studies of blood and bone marrow are indicated to establish a definite diagnosis.

**Q** *Is there any way for me to determine whether or not my patient with carcinoma of the stomach, associated with hepatomegaly, has metastases to the liver?*

**A** The following procedures might be helpful. If the patient's alkaline-phosphatase level is elevated, the probability is great that the patient has metastatic cancer of the liver. Needle aspiration biopsy of the liver frequently reveals the presence of cancer cells. The technique is relatively simple but not entirely unassociated with the possibility of complications. Finally, peritoneoscopy might be considered as an alternative in this case to formal exploration.

**Q** *I have a patient, a 51-year-old man, with a rather diffuse roentgen-ray deformity of the stomach. A competent radiologist reports that roentgen-ray studies show either hypertrophic gastritis or cancer of the stomach. To make matters more complicated, this patient has achlorhydria. Repeated stool studies fail to reveal any evidence of occult blood. What further studies are indicated in the management of this patient?*

**A** This is an ideal situation for cytological study. If cells are reported Class I

or 2, it is certainly safe to watch the patient carefully, without advising surgery. A recent report refers to ten patients with hypertrophic gastritis, all of whom had exploratory operations for suspected neoplasm of the stomach. An interesting aspect of this condition is that the deformity of the stomach will remain unchanged over a period of years, despite treatment of any kind. If the roentgenographic abnormality is diffuse, benign hypertrophic gastritis is likely. If the abnormality is localized, it may be impossible to differentiate it from gastric cancer except as just suggested or by exploratory operation.

**Q** *A 46-year-old white woman has consulted me about a history of a lump in the breast of four weeks' duration, to her knowledge, discovered by self-examination. I find a 3-cm., smooth, round, freely moveable mass in the right upper quadrant of the right breast. There is no evidence of skin fixation and no palpable axillary lymph nodes. It is my impression that this process represents a benign cyst, but it seems a little hard. Should aspiration be performed?*

**A** Upon careful review of the patient's history, if this is the first such mass that has been detected, it should be classified as a "dominant lump" and removed surgically. Occasionally such a procedure may reveal a small carcinoma. It also gives a clue to the possible breast-disease "fu-

ture" for this patient. With microscopic evidence of benignity in this first cyst, future similar "dominant lumps" may safely be aspirated. If this patient, however, gives a history of previous removal of a cyst, review of the slide will be helpful in planning treatment for the lump now under consideration. If aspiration is performed and residual mass persists, a local excision of the area should be done and the tissue studied microscopically. If no fluid, or if bloody fluid, is obtained on aspiration, a local excision and examination should be done to rule out the possibility of cancer.

**Q** *Which moles, occurring in adults, should be excised as potentially malignant lesions?*

**A** Any nevus subjected to continued irritation and trauma should be removed. In general, all pigmented moles that occur on the palms of the hands, the soles of the feet, or the genitalia must be presumed to be junctional nevi, compound nevi, or melanocarcinoma and should be removed, since melanocarcinoma of the skin or mucous membranes is thought to arise from junctional or compound nevi. The common mole or intradermal nevus probably does not undergo cancerous change. These benign intradermal nevi do not occur, or do so with exceeding rarity, on the palms, soles, or genitalia. Any nevus undergoing change in size or color is best excised and studied microscopically.

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#### References to the Cigarette Etiology of Lung Cancer In Previous Issues of CA

- 2:97, May, 1952      Tobacco and lung cancer.
- 4:47, March, 1954    The place of tobacco in lung-cancer etiology.
- 4:49, March, 1954    The place of tobacco in the etiology of lung cancer.



## new developments in cancer

### **Eel Anticoagulant . . .**

The oral glands of some eels are rich in an extremely powerful anticoagulant, many times as active as heparin. George Y. Shinowara and others in the Department of Pathology at Ohio State University, who discovered the substance (as yet unisolated and unpurified), have found evidence that it may interfere with the conversion of fibrinogen to fibrin, the final step in blood clotting. The anticoagulant is inhibited by protamine, a chain of a few amino acids. Blood-sucking lampreys from various parts of the United States elaborated vastly different amounts of the anticoagulant. Some had none at all. If the compound proves useful clinically, the eels will have made some slight restitution for their devastation of Great Lakes and Pacific fisheries.

### **Advantages and Disadvantages . . .**

Nutrition studies by Gerald J. Cox of the University of Pittsburgh provide intellectual food for philosophers. The research—in rats—indicates that man lives not by bread alone. Cox grows the biggest rats in the world. Among the measures taken to produce giant rats are:

Pregnant animals are given the most nu-

tritious stuff the mind of man and appetite of rat can devise, and the expectant mothers are taken out of their cages three times a day and petted.

The smaller offspring rats gradually are weeded out so that more mothers are available to nurse fewer large offspring—eventually mothers, nursing in relays, have only two offspring each for their rich and abundant milk supply.

Mothers during pregnancy and their offspring in embryonic and postnatal life are given every other advantage science can provide. So what happens? Cox gets his big rats. The largest are twice the size of normal rats and they are solid with muscle and bone. But the petted and pampered mothers exhibit a cannibalistic appetite and, with a love of good red meat, frequently eat their young. The young, after a fleeting period of pride in their enormous size and great strength, come to a most inglorious destiny. These big, handsome, meat-eating brutes see their solid flesh suddenly turn into rolls of fat; the males become impotent and sterile; their hair turns gray (this can be corrected with a more diversified diet containing copper); their third molars frequently decay; and, if they follow the course of fat animals observed by other scientists—and they seem to be doing this—they will be subject

to many diseases, including cancer, and a short life. In other experiments, Cox has his rats eat at "first table"—that is, one group always nurses first and the other group always takes what's left. The "first table" clientele weigh 40 per cent more than the others; but the "second table" set enjoy excellent health and active lives.

### ***Kinetin and Growth . . .***

Of possible major scientific importance (and perhaps of potential clinical value also) was the discovery by University of Wisconsin scientists of kinetin, a simple substance that makes cells divide. Derived from deoxyribonucleic acid (DNA), kinetin has a molecular weight of 215— $C_{10}H_{15}N_5O$ . Its surprising simplicity suggests that it may play a leading role in growth. It also lends itself to production of analogues as potential blocking agents—a prime target in cancer chemotherapy. When added to a culture of plants long past the growth stage, kinetin makes aged cells rejuvenate and divide. When the plant-growth hormone, auxine (which makes cells elongate), is in the culture medium along with kinetin, the cells divide indefinitely. When the growing cells are transferred to a new medium that lacks kinetin, growth stops. Kinetin's discovery and isolation in pure crystalline form were the work of Folke Skoog and Carlos Miller of the Department of Botany and F. M. Strong and Malcolm von Salza of the Department of Biochemistry.

### ***Immunity and Cancer . . .***

Scattered bits of research are indicating that loss of immunity is associated with the development of cancer. Whether this property is one of cause or effect is anyone's guess. It probably is a sign of susceptibility. Samuel Albert and Ralph M. Johnson of the Detroit Institute of Cancer Research have found that mice susceptible

to certain cancers progressively lose their ability to form antibodies as they approach the age when cancer develops. Animals, even those of the same strain, that do not develop cancer retain their antibody-synthesizing powers. In one series of tests, the scientists injected radioactive phosphorus into mice and checked its uptake by antibody-producing lymph nodes. Then transplants of breast cancer were made. The transplants took and killed animals whose nodes had taken up little phosphorus; in animals with a strong uptake, the transplants were destroyed. Phosphorus uptake by the thyroid, adrenals, and gonads was considered an indication of endocrine activity. Animals with active glands proved much more resistant to both transplanted and spontaneous cancer than those with apathetic glands. Phosphorus uptake by nodes and glands was compared with the animals' production of gamma-globulin in response to injection with antigenic substances. There was a direct correlation. Gamma-globulin production gradually dropped off, just as phosphorus uptake did, as susceptible animals approached the cancer age. These observations have afforded a high degree of accuracy in predicting which animals would die of cancer.

### ***"Guided Missiles" Against Cancer . . .***

Tyrosine, the thyroxine precursor, has been labeled strongly with radioactive iodine and fed to melanoma patients. The melanomas preferentially took up the labeled material; but they did not take up enough of it to destroy the tumors. William H. Beierwaltes of the University of Michigan who performed these experiments on eight human patients now has turned back to melanotic mice for some basic answers. He is removing the mouse thyroid to determine whether in these animals the tumors' uptake of radioactive tyrosine can be increased.

mal risk of developing mouth cancer, and if nonsmoking drinkers run five times the normal risk, drinking smokers have twenty-five times the normal chance of mouth cancer. In terms of pure alcohol content, he said, French adults drink an annual average of 34 liters; Italians, 18 liters; Swiss, 16 liters; Belgians, 12 liters; North Americans, 8 liters; English, 6 liters; and Germans, 5.5 liters.

Lauffer (U. of Pittsburgh) says viruses (bacteriophage) change according to their environmental pH. They sediment quickly in a slightly acid medium, slowly in a neutral medium; and the process seems to be reversible without damage to the particles. He feels the viruses may either: (1) clump into larger units or break up into fragments; (2) take up or lose water, or (3) change shape by altering their surfaces. His studies indicate that (3) may be the answer.

Fain and Rosenblatt (Foster D. Snell) reported that nicotine is filtered out of cigarettes in diminishing quantities as the cigarettes are smoked. At three sevenths of the original length of the cigarette, 36 per cent of the nicotine is filtered out and at two sevenths, 25 per cent. A filter removed 9 per cent of the smoke nicotine -- an equal length of tobacco removed 8 per cent.

Breast-cancer incidence varies with socioeconomic status, family size, and geography, a survey of sixteen world areas indicates. Some findings are:

In Japan and other countries, says Segi (Sendaishi), breast-cancer patients usually have few if any children, short duration of milk secretion, and inability or unwillingness to nurse offspring.

Stocks (Colwyn Bay, North Wales) found that in England and Wales breast-cancer deaths among single women were 40 per cent higher than among married and widowed women. Later he found that the proportion of breast-cancer cases diminished with the increasing size of family.

Clemmesen (Copenhagen) found breast-cancer rates low and cervical-cancer rates high for women with large families. Cervical cancer seemed to depend upon sexual activity more than upon number of children -- it is high among Copenhagen prostitutes. In Thailand, where women usually nurse their children, breast cancer is 12.8 per cent of all cancers in women. It is 17 to 20 per cent in Western Europe and North America.

Marsden (Kuala Lumpur) noted that a high percentage (2 to 3) of all breast cancers detected in Malaya, Ceylon,

and East Africa are in males. Cirrhosis and consequent failure of the liver to inactivate circulating estrogens may be the cause.

Schiller (Evanston, Ill.) and Christopher (Holy Cross Hospital, Detroit) state that other authors have reported biopsy-proved cervical noninvasive carcinomas in pregnant women disappeared following delivery.

A review of the smoking-cancer literature by Ringertz (Stockholm) includes such observations as: (By Daff and Kennaway) the arsenic content of thirty-one different brands of cigarettes ranged from 0 to 100 micrograms per cigarette -- highest in American and lowest in Turkish brands. A person who smokes ten cigarettes a day inhales in one year a maximum of 36.5 mg. arsenic, which is about the amount an English large-town resident accumulates from the atmosphere over a lifetime. (By Correa, Roffo chemist) Phenanthrene, anthracene, and benzpyrene have been identified in cigarette tars distilled at 380° C. (This was not confirmed.)

Winship (Garfield Memorial Hospital, Washington), in a review of 262 known cases of childhood thyroid carcinoma, reported that 10 per cent had been irradiated for an enlarged thymus, but he expressed doubt that the small amount of radiation to this target could have caused the cancer.

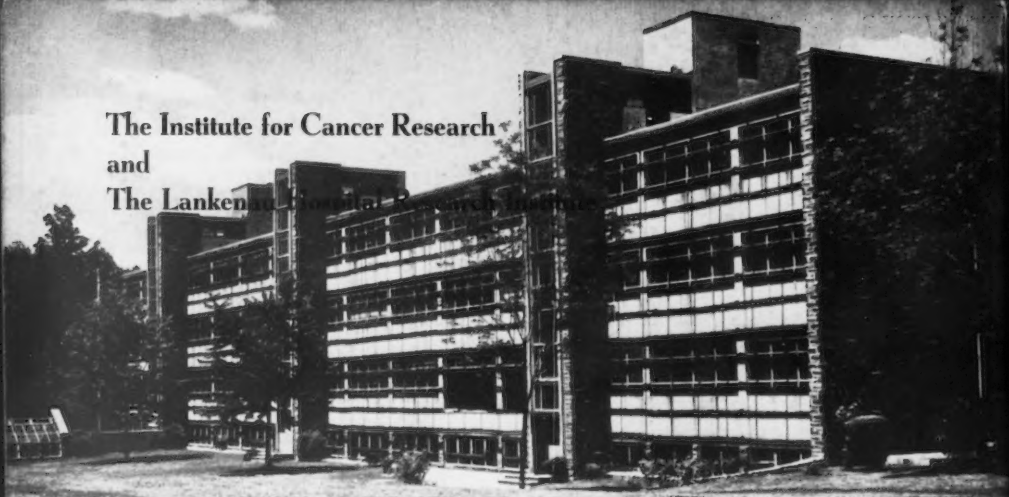
Bonser (Leeds) reported that many of 192 iron miners in the northwest part of England, on autopsy, showed deposition of iron ore in their lungs. Of them, fifty-nine had a severe degree of fibrosis. Cosmic rays and silicosis are suspected as causes of lung cancer among these men. She said anti-dust measures have brought a degree of control for lung cancer among asbestos workers.

Custer (U. of Pennsylvania) has listed more than seventy drugs as having an adverse effect on bone marrow, particularly nitrogen mustards and other new antileukemia preparations. Sulfonamides, he has reported, have brought about aplastic or hemolytic anemia in some sensitive individuals.

## COMING MEDICAL MEETINGS

<b>Date 1955</b>	<b>Meeting</b>	<b>City</b>	<b>Place</b>
May 16-19	American Urological Association	Los Angeles	Biltmore Hotel
May 23-26	International Surgical Congress	Geneva, Switzerland	
June 2-5	American College of Chest Physicians	Atlantic City	Ambassador Hotel
June 6-10	American Medical Association	Atlantic City	Auditorium
June 20-22	Canadian and British Medical Associations, Joint Meeting	Toronto, Ontario	Royal York Hotel
Aug. 8-11	National Medical Association	Los Angeles	
Sept. 12-15	International College of Surgeons	Philadelphia	Convention Hall
Sept. 19-22	American Hospital Association	Atlantic City	
Sept. 20-23	American Roentgen Ray Society	Chicago	Palmer House
Sept. 20-26	World Medical Association	Vienna, Austria	
Oct. 17-20	American Dental Association	San Francisco	Civic Auditorium
Oct. 30- Nov. 4	American College of Surgeons	Chicago	Conrad Hilton Hotel
Nov. 1-4	Interstate Postgrad. Med. Association of North America	Minneapolis	
Nov. 7-9	Association of Military Surgeons	Washington, D. C.	
Nov. 14-17	Southern Medical Association	Houston, Texas	
Dec. 11-16	Radiological Society of North America	Chicago	
Dec. 12-14	American Academy of Obstetrics and Gynecology	Chicago	Conrad Hilton Hotel

## The Institute for Cancer Research and The Lankenau Hospital



## INSTITUTIONS FOR

THE Lankenau Hospital Research Institute was established in 1925 as a department of the Lankenau Hospital in Philadelphia. In the first laboratory building, given by Mr. Rodman Wanamaker of Philadelphia and dedicated in 1925, work was begun on several pieces of the big problem—"What are the chemical factors controlling growth and development, both normal and abnormal?"

A staff of six were the original workers gathered together with the philosophy that cancer, ramifying into many directions, should be attacked through the media of many disciplines. As the staff was gradually expanded, new techniques were added. By 1944 the staff outgrew the original building and various groups worked across the street from the hospital in improvised laboratories, until a new building, the gift of the Pew Memorial Foundation, was ready for occupancy in November, 1949. In 1944 another corporation was formed, called "The Institute for Cancer Research," as one of the phenomena of the growth of the Lankenau Hospital Research Institute. The two corporate entities occupy the building in Fox Chase, Philadelphia, but the staff of approximately ninety scientific workers and forty in administration and maintenance work as a unified group.

The building is completely equipped for research in various branches of biology, chemistry, pathology, and physics, including departments of chemotherapy, embryology, experimental pathology, experimental zoology, genetics and cytochemis-

try, general biochemistry, metabolic chemistry, physiological chemistry, and physics.

Separate from the main building is an animal house with a capacity of 50,000 mice per year and approximately 10,000 rats—the main animals; among others used are *Drosophila* and frogs. Greenhouse facilities are also present for the study of growth phenomena in plants.

There is a close liaison with the Lankenau Hospital, in which the Department of Clinical Oncologic Research functions as a division of the hospital, using its facilities—including clinical laboratories, irradiation, and a special cobalt theratron. Consultation with the various specialists on their respective services is a daily occurrence. In addition, clinical facilities are offered in the Jeanes Hospital and Hahnemann Medical College and Hospital. Various members of the research staff teach in Temple University, University of Pennsylvania, and Hahnemann Medical College.

An excellent working library is provided, as well as instrument shops and other special facilities needed in the operation of a present-day research laboratory.

Seminars, at which both visiting scientists present their data and views and members of the staff give reports on work in progress, are held at regular intervals.

Arrangements are present for fellowships. During the past years we have had visiting scientists on fellowship bases from many parts of the world.

STANLEY P. REIMANN, M.D., Sc.D.  
Director and Scientific Director

## CANCER RESEARCH

